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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **04-095.478**
Solicitud de patente a nombre de **ELAN PHARMACEUTICALS, INC.**

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **ELAN PHARMACEUTICALS, INC.**, domiciliada en California, Estados unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 2675 notificado por fijación en lista el 6 de marzo de 2009, relacionado con el concepto técnico de fondo No. 381, nos permitimos manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio que ahora consta de 13 cláusulas y en las cuales se realizaron las siguientes modificaciones:

1.1 Se canceló la antigua reivindicación 3 que hacía referencia a la forma de dosificación.

1.2 Se canceló dentro de la antigua reivindicación 1 la expresión "*o un fragmentos inmunológicamente activo del mismo*".

1.3 De igual manera, se redactó de nuevo la antigua reivindicación 2 con el fin que la frase: "*la cual es una preparación oral*" sea una característica de los excipientes que participan dentro de la composición de la invención.

1.4 En la antigua reivindicación 5 se canceló la expresión "entre otros" que restaba claridad a la reivindicación.

1.5 En la antigua reivindicación 8 (nueva cláusula 7) se canceló la frase "*los cuales se pueden formular de tal manera que permitan una liberación sostenida del ingrediente activo*."

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1.6 Se modificó la antigua reivindicación 9 con el ánimo de especificar que la composición puede comprender además propelantes presurizados aceptables.

1.7 La antigua reivindicación 11 (nueva cláusula 10) se redactó de tal manera que se entienda que la composición de la invención puede contener además excipientes adecuados para la forma de supositorio.

1.8 Se eliminó la antigua reivindicación 12.

1.9 Se canceló el término ambiguo “cerca de” dentro de la antigua reivindicación 13.

En cuanto a estas modificaciones me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

Teniendo en cuenta el concepto técnico emitido por el Señor Superintendente Delegado para la propiedad intelectual, Gian Carlo Marcenaro Jiménez, a la doctora Ana Maria Castro Wey, el cual fue radicado el día 4 de marzo de 2009 bajo el No. 09-012566, no se presenta una tasa adicional, toda vez que el nuevo capítulo reivindicatorio comprende menos de 15 reivindicaciones.

2. Claridad de la solicitud

Sobre este particular, nos permitimos manifestar que con la cancelación de la expresión relacionada con los fragmentos activos del anticuerpo monoclonal, queda cabalmente superada la objeción en cuanto a dicha reivindicación.

De otra parte, en cuanto a la reivindicación 2, nos permitimos señalar que con la nueva redacción es claro que dicha reivindicación es de producto.

En relación con las antiguas reivindicaciones 8 a 13, el señor examinador podrá notar que con la nueva redacción dichas cláusulas se encuentran caracterizadas por los elementos que la constituyen. De igual forma, las antiguas reivindicaciones 13 y 14 también quedan claras, toda vez que se canceló la expresión “se formula”.

3. Nivel inventivo

Sobre este particular, el señor examinador manifiesta que la composición que contiene natalizumab es evidente a partir de lo divulgado en los documentos D1 y D2.

373
373

Clarke, Modet & C^o

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3

Sobre este particular, atentamente nos permitimos decir que las dos referencias citadas por ese despacho no revelan ni sugieren una composición de las características del nuevo capítulo reivindicatorio, es decir, composiciones que puedan ser útiles para la administración crónica del natalizumab. De hecho, la composición de la solicitud en estudio proporciona de manera sorprendente un mantenimiento de la supresión crónica de la inflamación por esclerosis múltiple (de sus siglas en inglés MS).

Se había observado que el cese del régimen de dosificación repetido causaba la anulación de la supresión de la inflamación. En efecto, los tratamientos con composiciones del arte previo para la inhibición de la inflamación, requerían de regímenes de dosificación totalmente diferentes, toda vez que la administración de dichas composiciones podía causar una reacción de respuesta del propio sistema del cuerpo, lo cual podía conducir a un reconocimiento de la inflamación como un alivio patológico y crónico resultante de la inflamación patológica.

Es así, que de manera sorprendente, la composición de la invención en estudio muestra un perfil ventajoso en un régimen de dosis crónico no sólo por ser más efectiva que un régimen de tiempo corto, sino también porque se logra mantener la supresión de la inflamación patológica. Este resultado no habría podido ser esperado por una persona medianamente versada en la técnica, es decir, que niveles del agente integrina anti-alfa-4 que se mantengan durante un número de meses o incluso de años.

Así las cosas, si la persona versada en la materia correspondiente tuviera acceso a las enseñanzas de los dos documentos citados por ese despacho, no podría evidenciar o derivar de manera evidente las ventajas de la composición reclamada para la administración crónica del natalizumab para periodos de al menos 6 meses, dado que si bien D1 y D2 reportan composiciones de diversas formas farmacéuticas que contienen anticuerpos monoclonales del tipo natalizumab, también es cierto, que ninguna de estas anterioridades muestra una composición que contenga un estabilizador y un portador que sean útiles para las cantidades de natalizumab que se revelan en el capítulo reivindicatorio ahora modificado.

Adicionalmente, es deseo del solicitante poner en consideración de ese despacho la publicación de Munschauer y colaboradores titulada "*Natalizumab Significantly increases the Cumulative Probability of Sustained Improvement in Physical Disability*", la cual muestra que la administración crónica de una composición de la invención **anula la parálisis en sujetos**. Sobre este particular, atentamente dirigimos la atención del señor examinador a las figuras 1 a 4 de dicha publicación, que presentan datos relacionados con el mejoramiento sostenido en la discapacidad física en los pacientes. Es más, en la parte de "conclusiones" se establece que "*este análisis proporciona la primera evidencia que el natalizumab se encuentra asociado con el*

3

374
374

Clarke, Modet & C^o

COLOMBIA

4

mejoramiento significativo en el efecto funcional más que la progresión disminuida o prevención de la discapacidad en un grupo de pacientes con MS recurrente."

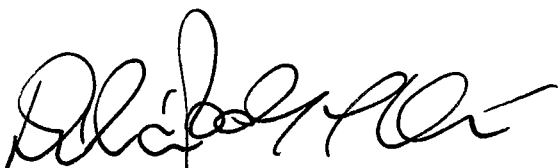
Lo anterior, también puede corroborarse en el Artículo de Polman y colaboradores, titulado "*A randomized, placebo-controlled trial of Natalizumab for relapsing Multiple sclerosis*", del cual también nos permitimos adjuntar una copia informal, donde se muestran datos adicionales del estudio AFFIRM.

Por las razones expuestas anteriormente, atentamente nos permitimos señalar que a la luz de las modificaciones realizadas en el capítulo reivindicatorio, la invención en estudio cumple cabalmente con los requisitos de patentabilidad, especialmente con el de nivel inventivo.

Habiendo atendido cabalmente las objeciones presentadas por ese despacho, atentamente solicitamos se conceda el privilegio de patente de invención a la solicitud en estudio o si el examinador considera que subsisten razones para objetar la presente invención, rogamos expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que nuestro mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: "*habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares*" y "*(.) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso*", respectivamente (El subrayado es nuestro).

En consecuencia, pedimos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional

Señor Superintendente,


DILIA RODRIGUEZ D' ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.

THE UNIVERSITY OF CHICAGO

DEPARTMENT OF THE HISTORY OF ARTS AND ARCHITECTURE

THE HISTORY OF ARTS AND ARCHITECTURE
IN THE MIDDLE AGES
BY
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378
378

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A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Natalizumab is the first α_4 integrin antagonist in a new class of selective adhesion-molecule inhibitors. We report the results of a two-year phase 3 trial of natalizumab in patients with relapsing multiple sclerosis.

METHODS

Of a total of 942 patients, 627 were randomly assigned to receive natalizumab (at a dose of 300 mg) and 315 to receive placebo by intravenous infusion every four weeks for more than two years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability, as measured by the Expanded Disability Status Scale, at two years.

RESULTS

Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77; $P < 0.001$). The cumulative probability of progression (on the basis of Kaplan-Meier analysis) was 17 percent in the natalizumab group and 29 percent in the placebo group. Natalizumab reduced the rate of clinical relapse at one year by 68 percent ($P < 0.001$) and led to an 83 percent reduction in the accumulation of new or enlarging hyperintense lesions, as detected by T_2 -weighted magnetic resonance imaging (MRI), over two years (mean numbers of lesions, 1.9 with natalizumab and 11.0 with placebo; $P < 0.001$). There were 92 percent fewer lesions (as detected by gadolinium-enhanced MRI) in the natalizumab group than in the placebo group at both one and two years ($P < 0.001$). The adverse events that were significantly more frequent in the natalizumab group than in the placebo group were fatigue (27 percent vs. 21 percent, $P = 0.048$) and allergic reaction (9 percent vs. 4 percent, $P = 0.012$). Hypersensitivity reactions of any kind occurred in 25 patients receiving natalizumab (4 percent), and serious hypersensitivity reactions occurred in 8 patients (1 percent).

CONCLUSIONS

Natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing multiple sclerosis. Adhesion-molecule inhibitors hold promise as an effective treatment for relapsing multiple sclerosis. (ClinicalTrials.gov number, NCT00027300.)

From the Vrije Universiteit Medical Center, Amsterdam (C.H.P.); St. Michael's Hospital, Toronto (P.W.O.); General Teaching Hospital, Prague, Czech Republic (E.H.); St. Vincent's University Hospital, Dublin, Ireland (M.H.); University Hospital Basel, Basel, Switzerland (L.K.); Institute of Neurology, London (D.H.M., G.G.); Texas Neurology, Dallas (J.T.P.); Mt. Sinai School of Medicine, New York (F.D.L.); Silesian Medical University, Katowice, Poland (A.W.); and Biogen Idec, Cambridge, Mass. (M.T., F.L., M.A.P., A.W.S.). Address reprint requests to Dr. Polman at the VU Medical Center, P.O. Box 7057, Amsterdam 1007 MB, the Netherlands, or at ch.polman@vumc.nl.

*Additional members of the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study group are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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379
379

RELAPSING MULTIPLE SCLEROSIS IS CHARACTERIZED by the intermittent development of inflammatory lesions in the brain and spinal cord, resulting in plaques of demyelination and axonal loss. Lymphocyte migration across the blood-brain barrier is thought to be an important early step in the formation of lesions.¹ The interaction of $\alpha_4\beta_1$ integrin, a protein on the surface of lymphocytes, with vascular-cell adhesion molecule 1 (VCAM-1), which is expressed on the surface of vascular endothelial cells in brain and spinal cord blood vessels, mediates the adhesion and migration of lymphocytes in areas of inflammation.²⁻⁶ Furthermore, the interaction of $\alpha_4\beta_1$ integrin with ligands such as fibronectin³ and osteopontin⁷ may modulate the survival, priming, and activation of leukocytes that have gained access to the parenchyma of the central nervous system.⁸⁻¹¹ Natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals), which belongs to a new class of selective adhesion-molecule inhibitors, binds to the α_4 subunit of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and blocks binding to their endothelial receptors (VCAM-1 and mucosal addressin-cell adhesion molecule 1, respectively), thereby attenuating inflammation.¹² Natalizumab may also modulate ongoing inflammatory reactions by inhibiting the binding of α_4 -positive leukocytes with fibronectin and osteopontin.

Current therapies for multiple sclerosis, including interferon beta and glatiramer acetate, are only moderately effective, reducing the annualized rate of relapse by about one third.¹³⁻¹⁶ On the basis of the favorable results of a phase 2 trial of natalizumab in patients with relapsing multiple sclerosis,¹⁷ a two-year phase 3 clinical trial, the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study, was initiated to confirm the efficacy of natalizumab in relapsing multiple sclerosis and to evaluate the safety of long-term treatment.

METHODS

PATIENTS

Ninety-nine clinical centers in Europe, North America, Australia, and New Zealand enrolled 942 patients beginning on November 6, 2001. All patients gave written informed consent. The study protocol was developed by the investigator advisory committee and sponsors, was approved by central and local ethics committees, and was

overseen by an independent safety-monitoring committee. Study data were collected by the investigators and an independent organization (PPD International) and were held and analyzed by Biogen Idec and Elan Pharmaceuticals. All members of the publication committee had full access to the data. During the study, the investigator advisory committee and sponsor representatives met at least monthly to discuss study progress. The manuscript was written by Drs. Polman and Panzara, with input from all coauthors. All authors vouch for the veracity and completeness of the data and data analysis.

Enrollment was limited to men and women who were between the ages of 18 and 50 years and had a diagnosis of relapsing multiple sclerosis¹⁸; who had a score of 0 to 5.0 on the Expanded Disability Status Scale (EDSS), a rating that ranges from 0 to 10, with higher scores indicating more severe disease¹⁹; who had undergone magnetic resonance imaging (MRI) showing lesions consistent with multiple sclerosis; and who had had at least one medically documented relapse within the 12 months before the study began. Patients with disease that was categorized as primary progressive, secondary progressive, or progressive relapsing were excluded.²⁰ Additional exclusion criteria included the following: a relapse within 50 days before the administration of the first dose of the study drug, treatment with cyclophosphamide or mitoxantrone within the previous year, or treatment with interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or intravenous immune globulin within the previous 6 months. Patients who had received treatment with interferon beta, glatiramer acetate, or both for more than six months were also excluded.

STUDY DESIGN AND RANDOMIZATION

Patients were randomly assigned in a 2:1 ratio to receive either natalizumab (at a dose of 300 mg) or placebo by intravenous infusion every 4 weeks for up to 116 weeks. Patients were randomly assigned to treatment that was stratified according to study site in blocks of three (two active, one placebo) with the use of a computer-generated block randomization schedule and a multidigit identification number, implemented by an interactive voice-response system. All study personnel, patients, sponsor personnel involved in the conduct of the study, and the investigator advisory

9

388
300

committee were unaware of treatment assignments throughout the study.

STUDY PROCEDURES AND END POINTS

At each study site, primary and backup examining neurologists and primary and backup treating neurologists were designated. Treating neurologists were responsible for all aspects of patient care, including the management of adverse events and the treatment of relapsing disease. Examining neurologists performed objective evaluation with use of the EDSS and neurologic examination during all study visits; they were not in contact with patients in any other capacity, so as to reduce the possibility of being unblinded by side effects or laboratory assessments.

Patients visited the clinic every 12 weeks for scoring on the EDSS, blood chemical and hematologic analyses, evaluation of adverse events, and testing for anti-natalizumab antibodies. Patients were also seen by the treating neurologist at unscheduled visits within 72 hours after the onset of new neurologic symptoms. If a relapse was suspected, the patient was referred to the examining neurologist, who evaluated the patient within five days after the event. Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist. At the discretion of the treating neurologist, relapses were treated with intravenous methylprednisolone at a dose of 1000 mg per day for three or five days. Patients whose disability progression was sustained for 12 weeks were allowed to continue participation in the study and were given the option of adding an available treatment for multiple sclerosis as rescue medication per protocol while continuing to receive the study drug. Patients were strongly encouraged to remain in the study for follow-up assessments even if they had discontinued the study drug.

Proton-density-weighted or T₂-weighted and gadolinium-enhanced T₁-weighted MRI scans of the brain were obtained at baseline, at week 52, and at week 104. Contiguous, 3-mm-thick axial slices through the whole brain were acquired. MRI analysis was performed at the Central Reading Center at the Institute of Neurology, University College London, by experienced raters who were unaware of treatment assignment.

The study had primary and secondary end

points at two prespecified times. An assessment of the inflammatory characteristics of the disease was performed at one year and of the progression of the irreversible destructive process at two years. At one year, the primary end point was the rate of clinical relapse, and secondary efficacy end points were the number of new or enlarging hyperintense lesions as detected by T₂-weighted MRI, the number of lesions as detected by gadolinium-enhanced MRI, and the proportion of relapse-free patients. At 2 years, the primary end point was the cumulative probability of sustained progression of disability, which was defined as an increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse). Secondary efficacy end points at two years were the rate of clinical relapse, the volume of lesions as detected by T₂-weighted MRI, the number of new hypointense lesions as detected by unenhanced T₁-weighted MRI, and the progression of disability as measured by the Multiple Sclerosis Functional Composite. This report presents data on the one-year and two-year primary end points and the one-year secondary end points for which data were also available at two years.

Binding antibodies against natalizumab were assessed with the use of an enzyme-linked immunosorbent assay. Samples that were positive for binding antibodies (0.5 µg per milliliter) were further tested by flow cytometry to assess the ability of the antibodies to interfere with the binding of natalizumab to α₄ integrin.

STATISTICAL ANALYSIS

The estimate of sample size was based on data from previous trials of natalizumab¹⁷ and of interferon beta-1a¹³ with the use of two-sided tests, with an alpha level of 0.05. The annualized rate of relapse at one year was predicted to be 0.6 with natalizumab and 0.9 with placebo. For an annualized relapse rate, a likelihood-ratio test was used to determine the sample size required for 90 percent power (n=765), with a 2:1 ratio of natalizumab to placebo. With an assumed drop-out rate of 15 percent and rounding, the number of patients needed was estimated to be 900. In order to power the study for the two-year end point of disability progression, progression rates at the end of two years were assumed to be 34.9

10

381
381

percent for the placebo group and 22.7 percent for the natalizumab group. Simulations of the log-rank test for survival were run with 60 percent of the accrual in the first 24 weeks and the remainder in the next 24 weeks, assuming a 20 percent dropout rate over the 2-year study. The sample size of 900 provided 90 percent power with the use of a Bonferroni adjustment for multiple end points, maintaining the type 1 error rate of 0.05.

P values that are reported for most baseline demographic and disease characteristics were calculated with the use of a t-test to compare differences in means. The exceptions were sex, race, and diagnosis of multiple sclerosis by the McDonald criteria,¹⁸ for which a chi-square statistic was used to compare treatment groups.

The primary end point at two years was the cumulative probability of sustained progression of disability. This was assessed by an analysis of the time until the onset of the progression of disability that was sustained over 12 weeks with the use of the Cox proportional-hazards model. The annualized rate of relapse (the primary end point at one year) was calculated by Poisson regression; relapses that occurred after rescue treatment was initiated for patients who had had a sustained progression of disability (per protocol) were censored. The predefined statistical models included baseline scores on the EDSS for sustained progression of disability and the number of relapses in the previous year for the relapse rate. Additional baseline factors were tested for inclusion in each of the models, including the EDSS score (≤ 3.5 or > 3.5), the presence or absence of lesions as detected by gadolinium-enhanced MRI, the number of hyperintense lesions as detected by T₂-weighted MRI (< 9 or ≥ 9), and age (< 40 or ≥ 40 years).²¹⁻²³ Each covariate was tested in the model for statistical significance with the use of a backward-selection procedure, and only statistically significant covariates ($P \leq 0.10$) were included in the model. Only age was included in the final model for disability progression; the EDSS score, the presence or absence of lesions as detected by gadolinium-enhanced MRI, and age were included for the rate of relapse.

For the progression of disability, a sensitivity analysis was conducted on the change in EDSS scores that was sustained for 24 weeks. For the annualized relapse rate, sensitivity analyses were performed with and without censoring, as well

as with and without adjustment for significant covariates. The unadjusted relapse rate was calculated as the total number of relapses divided by the total number of patient-years followed for each treatment group. The Hochberg procedure²⁴ for multiple comparisons was used for the analysis of the two primary end points (the annualized relapse rate and the time to sustained progression of disability). Hence, the significance level was set so that if the higher of the P values for the analyses of these end points was ≤ 0.05 , then both end points were considered to be statistically significant; otherwise, the lower of the P values was tested at a significance level of 0.025.

Secondary efficacy end points were rank-ordered, and a closed testing procedure was used, so that if statistical significance was not achieved for an end point, end points of a lower rank were not considered to be statistically significant. Secondary efficacy end points were analyzed by logistic regression that included a term for the treatment group and the respective baseline measure as a covariate. In the analyses of secondary end points, missing values were imputed using the mean for the respective measures in the study population.

Differences between treatment groups with regard to adverse events were analyzed by the chi-square test, and serious adverse events were analyzed by Fisher's exact test. Poisson regression was used to calculate the difference between the rates of infection in each treatment group.

All analyses followed the intention-to-treat principle. All reported P values are two-tailed. The one-year analyses occurred when 900 patient-years of data had been collected. The date on which the database was locked for the two-year analyses was January 31, 2005, which resulted in 2076 patient-years of observation and 1338 patient-years of exposure to natalizumab.

RESULTS

STUDY POPULATION

Among the 942 patients, 627 were assigned to receive natalizumab and 315 to receive placebo. There were no significant differences in baseline characteristics between the treatment groups (Table 1). A total of 856 patients (91 percent) completed the 120-week study (Fig. 1), and 83 patients (a total of 9 percent, including 8 percent of patients in the natalizumab group and 10 percent

11

of those in the placebo group) withdrew from the study. Thirty-nine patients discontinued the study drug but completed follow-up (a total of 4 percent, including 4 percent of patients in the natalizumab group and 5 percent of those in the placebo group). Three patients who were assigned to receive placebo were never treated; these patients were included in the intention-to-treat efficacy analyses but were excluded from the safety analyses.

EFFICACY

A sustained progression of disability over two years (the two-year primary end point) was significantly less likely in the natalizumab group than in the placebo group (Fig. 2). At two years, the cumulative probability of progression (on the basis of Kaplan–Meier analysis) was 17 percent in the natalizumab group and 29 percent in the placebo group (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77; $P < 0.001$), which represents a decrease of 12 percentage points or a relative 42 percent decrease in the risk of a sustained progression of disability with natalizumab (Table 2). The sensitivity analysis of progression of disability that was sustained for 24 weeks yielded a 54 percent risk reduction in the natalizumab group (hazard ratio, 0.46; 95 percent confidence interval, 0.33 to 0.64; $P < 0.001$).

After one year of treatment, natalizumab reduced the annualized rate of relapse to 0.26 relapse per year, as compared with 0.81 relapse per year in the placebo group ($P < 0.001$) (Table 2). The 68 percent relative reduction in the annualized rate of relapse produced by natalizumab was maintained at two years ($P < 0.001$). Subgroup and sensitivity analyses showed results consistent with the primary analysis. The proportion of relapse-free patients was significantly higher in the natalizumab group than in the placebo group at one year (77 percent vs. 56 percent, $P < 0.001$) and at two years (67 percent vs. 41 percent, $P < 0.001$). Natalizumab reduced the risk of relapse over two years by 59 percent (hazard ratio, 0.41; 95 percent confidence interval, 0.34 to 0.51; $P < 0.001$). An analysis of relapse in 51 patients in the natalizumab group and 27 patients in the placebo group who discontinued the study drug showed a return to baseline disease activity when natalizumab therapy was stopped but no evidence of rebound; 25 relapses were reported by 15 patients in the natalizumab group (29 percent) after discontinuation of the study

medication, as compared with 13 relapses reported by 8 patients in the placebo group (30 percent), giving an annualized relapse rate of 0.495 for patients receiving natalizumab, as compared with a rate of 0.608 for those receiving placebo (data not shown).

Natalizumab reduced the mean number of new or enlarging hyperintense lesions detected by T_2 -weighted MRI over two years by 83 percent, as compared with placebo ($P < 0.001$) (Table 2). Over two years, no new or enlarging hyperintense lesions developed in 57 percent of patients in the natalizumab group, as compared with 15 percent of patients in the placebo group. In contrast, 68 percent of patients in the placebo group had at least three new or enlarging hyperintense lesions, as compared with only 18 percent of patients in the natalizumab group. Natalizumab reduced the mean number of lesions as detected by gadolinium-enhanced MRI by 92 percent as compared with placebo at both one year and two years ($P < 0.001$) (Table 2). In addition, lesions detected by gadolinium-enhanced MRI were absent in 97 percent of patients in the natalizumab group as compared with 72 percent of patients in the placebo group on MRI scanning at two years.

SAFETY

Over the course of the two-year study, 596 patients receiving natalizumab (95 percent) and 300 of the 312 patients receiving placebo (96 percent) reported at least one adverse event. As shown in Table 3, adverse events that were significantly more common in the natalizumab group were fatigue and allergic reaction. The most severe adverse events reported by patients were mild in 17 percent, moderate in 55 percent, and severe in 23 percent of patients in the natalizumab group and mild in 13 percent, moderate in 56 percent, and severe in 27 percent in the placebo group. Serious adverse events were observed in 19 percent of patients receiving natalizumab and in 24 percent of patients receiving placebo ($P = 0.06$); the most common serious adverse events were relapsing multiple sclerosis (6 percent with natalizumab and 13 percent with placebo; $P < 0.001$), cholelithiasis (<1 percent with natalizumab and <1 percent with placebo), and the need for rehabilitation therapy (<1 percent with natalizumab and <1 percent with placebo). Two deaths occurred during the study, both in the natalizumab group. One patient, who died of malignant melanoma,

387
382

12

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Natalizumab (N=627)	Placebo (N=315)	Total (N=942)	P Value
Age — yr				
Mean	35.6±8.5	36.7±7.8	36.0±8.3	0.056
Range	18–50	19–50	18–50	
Sex — no. of patients (%)				
Male	178 (28)	104 (33)	282 (30)	0.144
Female	449 (72)	211 (67)	660 (70)	
Race — no. of patients (%)†				
White	603 (96)	296 (94)	899 (95)	0.126
Other	24 (4)	19 (6)	43 (5)	
McDonald criteria — no. of patients (%)‡				
1 (≥2 attacks, ≥2 lesions)	528 (84)	261 (83)	789 (84)	0.938
2 (≥2 attacks, 1 lesion)	72 (11)	40 (13)	112 (12)	
3 (1 attack, ≥2 lesions)	18 (3)	10 (3)	28 (3)	
4 (1 attack, 1 lesion)	9 (1)	4 (1)	13 (1)	
Disease duration — yr				
Median	5.0	6.0	5.0	0.511
Range	0–34	0–33	0–34	
No. of relapses in past yr — no. of patients (%)				
0	6 (<1)	6 (2)	12 (1)	
1	368 (59)	180 (57)	548 (58)	
2	197 (31)	102 (32)	299 (32)	
≥3	56 (9)	27 (9)	83 (9)	
Mean	1.53±0.91	1.50±0.77	1.52±0.86	0.640
Range	0–12	0–5	0–12	
EDSS score — no. of patients (%)				
0	31 (5)	18 (6)	49 (5)	
1.0–1.5	179 (29)	94 (30)	273 (29)	
2.0–2.5	208 (33)	103 (33)	311 (33)	
3.0–3.5	130 (21)	63 (20)	193 (20)	
4.0–4.5	60 (10)	28 (9)	88 (9)	
5.0	17 (3)	7 (2)	24 (3)	
≥5.5	2 (<1)	2 (<1)	4 (<1)	
Mean	2.3±1.2	2.3±1.2	2.3±1.2	0.784
Range	0–6	0–6	0–6	

had a history of malignant melanoma and had noted a new lesion at the time of receiving the first dose of natalizumab; he had received a total of five doses of natalizumab before receiving a confirmed diagnosis. A second patient died of alcohol intoxication after having received 25 doses of natalizumab.

Infections were generally mild to moderate in severity and did not lead to drug discontinuation. The overall incidence of infection was 79 percent in each treatment group and occurred at a rate of 1 per patient-year in each group. When the rate was reanalyzed to include multiple occurrences of infection, it went up in each group,

384
384

Table 1. (Continued.)				
Characteristic	Natalizumab (N=627)	Placebo (N=315)	Total (N=942)	P Value
No. of lesions on gadolinium-enhanced MRI — no. of patients (%)				
0	307 (49)	170 (54)	477 (51)	
1	115 (18)	55 (17)	170 (18)	
2	66 (11)	24 (8)	90 (10)	
3	38 (6)	18 (6)	56 (6)	
≥4	100 (16)	46 (15)	146 (15)	
Missing data	1 (<1)	2 (<1)	3 (<1)	
Mean	2.2±4.7	2.0±4.8	2.2±4.7	0.511
Range	0–36	0–39	0–39	
No. of lesions on T ₂ -weighted MRI — no. of patients (%)				
<9	29 (5)	15 (5)	44 (5)	0.921
≥9	597 (95)	299 (95)	896 (95)	
Missing data	1 (<1)	1 (<1)	2 (<1)	

* Plus-minus values are means ±SD. EDSS denotes Expanded Disability Status Scale (range of scores, 0 to 10, with higher scores indicating more severe disease), and MRI magnetic resonance imaging. Percentages may not sum to 100, because of rounding.

† Race was determined at the time of enrollment by the treating investigator.

‡ Criteria are from McDonald et al.¹⁸

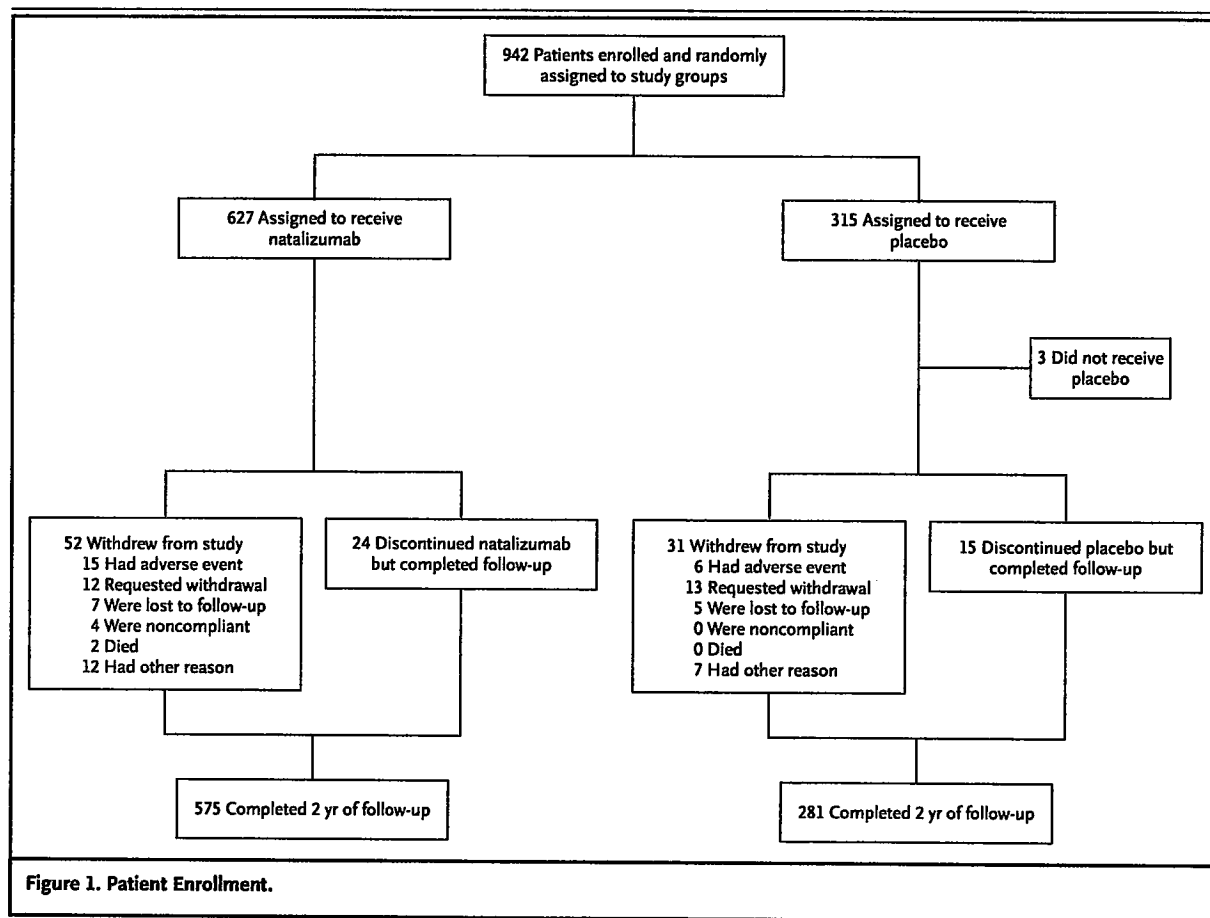
as expected. However, there remained no significant differences between the groups, with infections occurring at a rate of 1.52 per patient-year in the natalizumab group and 1.42 per patient-year in the placebo group ($P=0.32$). Common infections were nasopharyngitis (32 percent of patients receiving natalizumab and 33 percent of patients receiving placebo), influenza (17 percent and 16 percent, respectively), upper respiratory tract viral infection (13 percent and 15 percent), urinary tract infection not otherwise specified (13 percent and 12 percent), upper respiratory tract infection not otherwise specified (13 percent and 11 percent), and pharyngitis (12 percent and 10 percent). Serious infections occurred in 3.2 percent of patients receiving natalizumab and in 2.6 percent of patients receiving placebo. In the natalizumab group, the serious infections included four cases of pneumonia and five cases of urinary tract infection or urosepsis; the remaining infections that were reported as serious were of various causes and included pilonidal cyst infection, cellulitis, febrile infection, gastroenteritis, cryptosporidial diarrhea, mononucleosis, osteomyelitis, sinusitis, tonsillitis, viral infec-

tion, appendicitis, and an infection of unclear cause. In the placebo group, serious infections included two cases of appendicitis, two cases of gastroenteritis, and one case each of infection not otherwise specified, bladder infection, cystitis, and influenza.

A total of six cases of cancer were reported — one case (<1 percent) in the placebo group and five cases (<1 percent) in the natalizumab group. The five cases of cancer that occurred in natalizumab-treated patients included three cases of breast cancer, one case of stage 0 cervical cancer, and one case of newly diagnosed metastatic melanoma. There was one case of basal-cell carcinoma in the placebo group.

Infusion reactions were defined as any event that occurred within two hours after the start of the one-hour infusion; they were reported in 148 patients receiving natalizumab (24 percent) and in 55 patients receiving placebo (18 percent) ($P=0.04$). The most common infusion reaction was headache (5 percent with natalizumab and 3 percent with placebo). Most reactions were treated symptomatically and did not result in discontinuation of the study drug. Hypersensitivity reactions were

14

385
305

defined as reports of hypersensitivity, allergic reaction, or anaphylactic or anaphylactoid reaction by the investigator, as well as any report of urticaria, allergic dermatitis, or hives. The category was determined by the investigator on the basis of clinical judgment and severity. Twenty-five patients receiving natalizumab (4 percent) had 27 hypersensitivity reactions: 12 cases of urticaria or generalized urticaria, 1 of allergic dermatitis, 8 of a reaction called hypersensitivity, and 5 of anaphylactic or anaphylactoid reactions (urticaria plus other signs). One patient with a hypersensitivity reaction during the 7th infusion received other doses according to schedule and had an anaphylactic or anaphylactoid reaction during the 13th infusion. Fifteen reactions occurred on the second infusion. Eight hypersensitivity reactions (1.3 percent) were reported as serious adverse events among all patients receiving natalizumab, of which 5 reactions (0.8 percent) were considered serious systemic reactions (i.e., anaphylactic or anaphylactoid reactions).

Per protocol, the study drug was to be discontinued in all patients who had hypersensitivity reactions. Five of the eight patients with serious adverse events had respiratory or chest symptoms, but only one patient required supplemental oxygen. No cardiovascular compromise was associated with any of these events, although one patient did receive epinephrine. All patients recovered without sequelae.

Because of adverse effects, 6 percent of the patients receiving natalizumab and 4 percent of those receiving placebo discontinued the study drug, and 3 percent of patients receiving natalizumab and 2 percent receiving placebo withdrew from the study. There were no significant differences between treatment groups in the proportions of patients with clinically notable changes in laboratory values. Increases in the number of lymphocytes, monocytes, eosinophils, and basophils were seen in natalizumab-treated patients without elevations in the number of neutrophils.

15

These increases are consistent with expression of $\alpha_4\beta_1$ on these white-cell subgroups and are a known pharmacodynamic effect of natalizumab. Increases in nucleated red cells were also seen transiently in a small number of patients. All changes were reversible, were without clinical effects, and returned to baseline levels, usually within 16 weeks after the last dose was administered.

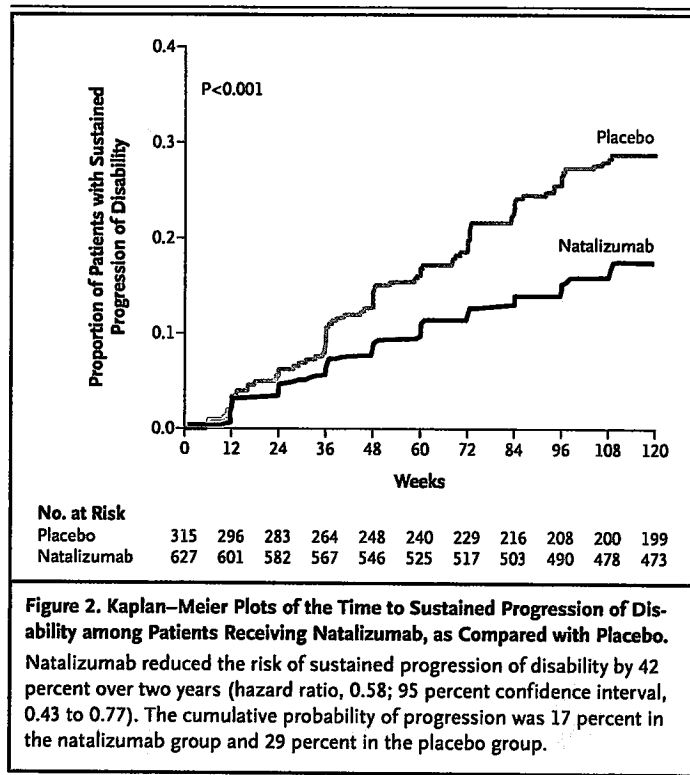
IMMUNOGENICITY

Fifty-seven patients receiving natalizumab (9 percent) had detectable antibodies at some time during the study. Of these 57 patients, persistent antibodies to natalizumab (antibodies detected at ≥ 2 times that were ≥ 42 days apart) developed in 37 patients (6 percent), who also had an increase in infusion-related adverse events and a loss of efficacy of natalizumab.

DISCUSSION

The results of AFFIRM support the hypothesis that the interaction between $\alpha_4\beta_1$ integrin and its targets is an important component of inflammation of the central nervous system in multiple sclerosis and that the disruption of these interactions and the resultant attenuation of inflammation are beneficial to patients. In patients with relapsing multiple sclerosis, natalizumab significantly reduced the risk of progression of disability and the annualized rate of relapse over two years of treatment. The effect of natalizumab was rapid in onset and was sustained. In addition, efficacy was observed in terms of all secondary end points (an 83 percent reduction in the number of lesions as detected by T_2 -weighted MRI and a 92 percent reduction in the number of lesions as detected by gadolinium-enhanced MRI) and all sensitivity analyses of the primary end points, indicating the robustness of the result.

Disease-modifying therapies have become the cornerstone of treatment for patients with relapsing multiple sclerosis. The two-year registration trials of the therapies that are currently available (interferon beta products and glatiramer acetate) have shown that these agents reduce the annualized rate of relapse by about one third.¹³⁻¹⁶ In addition, neither interferon beta-1b nor glatiramer acetate had statistically significant effects on the progression of disability in patients with relapsing disease.^{14,15} Hence, there remains a need



for more effective treatments for relapsing multiple sclerosis. The results of this study suggest that natalizumab may offer greater benefit to patients with relapsing multiple sclerosis than the other therapies.

The data presented here represent 30 percent of the placebo-controlled experience (patient-years of exposure) with natalizumab in patients with multiple sclerosis or Crohn's disease and 48 percent of the experience with natalizumab in patients with multiple sclerosis. In our study, natalizumab was safe as monotherapy over two years. In February 2005, all administration of natalizumab was voluntarily suspended by the manufacturers when they were notified of two cases of progressive multifocal leukoencephalopathy (PML). Both patients had received more than two years of natalizumab in combination with interferon beta-1a in a separate trial. Later, an additional case of PML was identified in a patient with Crohn's disease who had previously received a mistaken diagnosis of astrocytoma. The patient had received eight infusions of natalizumab. Detailed case histories of these three patients have been published elsewhere.²⁵⁻²⁷ An extensive safety evaluation of patients who received natalizumab

387

Table 2. End Points as Determined by Clinical Results and MRI Evaluation.*

End Point	1 Year			2 Years		
	Natalizumab (N=627)	Placebo (N=315)	P Value	Natalizumab (N=627)	Placebo (N=315)	P Value
Clinical						
Primary end point at 2 years: cumulative probability of sustained disability progression — %†	—	—		17	29	<0.001‡
Primary end point at 1 year: annualized relapse rate — mean (95% CI)§						
Preplanned interim analysis (after 900 patient-years)	0.26 (0.21–0.32)	0.81 (0.67–0.97)	<0.001	—	—	
Final analysis	0.27 (0.21–0.33)	0.78 (0.64–0.94)	<0.001	0.23 (0.19–0.28)	0.73 (0.62–0.87)	<0.001
Number of relapses — no. of patients (%)						
0	501 (80)	189 (60)		454 (72)	146 (46)	
1	106 (17)	76 (24)		123 (20)	65 (21)	
2	17 (3)	36 (11)		36 (6)	63 (20)	
≥3	3 (<1)	14 (4)		14 (2)	41 (13)	
Sensitivity analysis¶						
Adjusted annualized relapse rate	—	—		0.24	0.75	<0.001
Unadjusted annualized relapse rate	—	—		0.22	0.64	<0.001
Mean relapse rate per patient	—	—		0.22	0.67	<0.001
MRI						
	0–1 Year			0–2 Years		
Number of new or enlarging T ₂ -hyperintense lesions — no. of patients (%)			<0.001			<0.001
0	382 (61)	72 (23)		360 (57)	46 (15)	
1	112 (18)	41 (13)		106 (17)	32 (10)	
2	40 (6)	23 (7)		48 (8)	24 (8)	
≥3	93 (15)	179 (57)		113 (18)	213 (68)	
Number of new or enlarging T ₂ -hyperintense lesions						
Mean	1.2±4.7	6.1±9.0		1.9±9.2	11.0±15.7	
Median	0	3.0		0	5.0	
Minimum, maximum	0, 98	0, 77		0, 196	0, 91	
	At 1 Year			At 2 Years		
Number of gadolinium-enhancing lesions — no. of patients (%)			<0.001			<0.001
0	605 (96)	213 (68)		608 (97)	227 (72)	
1	17 (3)	42 (13)		12 (2)	39 (12)	
2	3 (<1)	15 (5)		1 (<1)	9 (3)	
≥3	2 (<1)	45 (14)		6 (<1)	40 (13)	
Number of gadolinium-enhancing lesions						
Mean	0.1±1.3	1.3±3.2		0.1±1.4	1.2±3.9	
Median	0	0		0	0	
Minimum, maximum	0, 32	0, 33		0, 32	0, 48	

* Plus-minus values are means ±SD. CI denotes confidence interval.

† Sustained disability progression was defined as an increase of 1.0 point or more in scores on the Expanded Disability Status Scale from a baseline score of 1.0 or more or an increase of 1.5 points or more from a baseline score of 0 that was sustained for 12 weeks.

‡ The hazard ratio for sustained progression of disability in the natalizumab group as compared with the placebo group was 0.58 (95 percent confidence interval, 0.43 to 0.77).

§ Relapses that occurred after sustained progression of disability was reached and rescue treatment was initiated (per protocol) were censored.

¶ Analysis includes relapses that occurred after sustained progression was reached and rescue treatment was initiated (per protocol).

|| The mean relapse rate per patient is the number of relapses for each patient divided by the total number of years of follow-up.

17

Table 3. Adverse Events.*

	Natalizumab (N=627)	Placebo (N=312)	P Value		Natalizumab (N=627)	Placebo (N=312)	P Value
	% of patients				% of patients		
Adverse event							
General condition					Menstrual disorder†		
Headache	38	33	0.137	Irregular menstruation or dysmenorrhea	7	4	0.102
Fatigue	27	21	0.048	Amenorrhea	2	1	0.405
Arthralgia	19	14	0.106	Neurologic condition			
Urinary urgency or frequency	9	7	0.365	Vertigo	6	5	0.779
Allergic reaction	9	4	0.012	Tremor	3	3	0.566
Chest discomfort	5	3	0.169	Serious adverse event‡			
Local bleeding	3	2	0.386	Relapse of multiple sclerosis	6	13	<0.001
Rigors	3	1	0.080	Cholelithiasis	<1	<1	0.435
Syncope	3	3	0.895	Need for rehabilitation therapy	<1	<1	0.999
Infection				Urinary tract infection, NOS	<1	0	0.308
Urinary tract	20	17	0.257	Depression	<1	<1	0.669
Lower respiratory tract	17	16	0.644	Anaphylactic reaction	<1	0	0.555
Gastroenteritis	11	9	0.328	Hypersensitivity reaction	<1	0	0.555
Vaginitis†	10	6	0.133	Fall	<1	<1	0.999
Tonsillitis	7	5	0.291	Breast cancer, NOS	<1	0	0.999
Psychiatric condition (depression)	19	16	0.197	Anaphylactoid reaction	<1	0	0.999
Gastrointestinal condition				Convulsion, NOS	<1	<1	0.604
Abdominal discomfort	11	10	0.561	Gastritis, NOS	<1	0	0.999
Abnormal liver-function results	5	4	0.406	Cervical dysplasia	<1	0	0.999
Skin				Alcohol poisoning	<1	<1	0.999
Rash	11	9	0.301	Head injury	<1	<1	0.999
Dermatitis	7	4	0.053	Thermal burn	<1	0	0.999
Pruritus	4	2	0.090				

* NOS denotes not otherwise specified.

† The percentage and P value were calculated on the basis of the number of female patients.

‡ Serious adverse events are listed only if they occurred in two or more patients in the natalizumab group.

in a clinical trial, also reported in this issue of the *Journal*, found no new confirmed cases of PML in patients treated with natalizumab.²⁸ (The results of another clinical trial of natalizumab — in this case, administered with interferon beta-1a — also appear in this issue.²⁹)

In conclusion, our study provides evidence that natalizumab significantly reduces the progression of disability and the occurrence of clinical relapse and suppresses the formation of lesions as visualized by MRI in patients with relapsing multiple sclerosis. Moreover, our data indicate that efficacy is realized early and persists throughout the treatment period. Within the 30-month evaluation period of this trial, natalizumab monotherapy had an excellent safety and tolerability profile. Continued assessments of long-term treatment with natalizumab will better define the safety

profile of this effective therapy and establish its place in the arsenal of treatments for relapsing multiple sclerosis.

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18

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CLINICAL TRIAL REGISTRATION

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389
389

19

REIVINDICACIONES

1. Una composición farmacéutica para tratamiento crónico de inflamación patológica en un paciente que comprende entre 0.1 a 10% de un anticuerpo monoclonal, tal como natalizumab, un estabilizador, un portador y/o un excipiente.
2. La composición de la reivindicación 1, caracterizada porque contiene aditivos seleccionados a partir del grupo que consiste de lactosa, manitol, almidón de maíz o almidón de papa; con ligadores, tales como celulosa cristalina, derivados de celulosa, acacia, almidón de maíz o gelatinas; con desintegradores, tales como almidón de maíz, almidón de papa o carboximetilcelulosa de sodio; con lubricantes, tales como talco o estearato de magnesio; y si se desea, con diluyentes, agentes amortiguantes, agentes humectantes reservativos y agentes saborizantes.
3. La composición de la reivindicación 1, caracterizada porque es el diluyente se selecciona del grupo que consiste de agua destilada, solución salina amortiguada con fosfato fisiológico, solución de Ringer, solución de dextrosa, y solución de Hank.
4. La composición de la reivindicación 2, caracterizada porque además comprende un adyuvante, preferiblemente

391
391

seleccionado del grupo que incluye hidróxido de aluminio, fosfato de aluminio, sulfato de aluminio, monofosforil 3 De-O-asilado lípido A (MPL™) , QS-21, aceite en emulsiones de agua (tal como escueleno o aceite de maní), opcionalmente en combinación con estimulantes inmunes, tales como monofosforil lípido A, y CPG.

5. La composición de la reivindicación 4, caracterizada porque además comprende otros agentes inmunoestimulantes específicos tales como MPL o 3-DMP, QS-21, aminoácidos poliméricos o monoméricos tales como ácido poliglutámico o polilicina, péptidos de muramilo.
6. La composición de una de las reivindicaciones anteriores, caracterizada porque es además incluye moléculas portadoras tales como proteoglicanos, glicosaminoglicanos tales como sulfato de heparina, ácido hialurónico, queratán-sulfato, condroitin 4-sulfato, condroitin 6-sulfato, heparán sulfato y dermatin sulfato, perlecan y pentopolisulfato.
7. La composición de la reivindicación 1, caracterizada porque contiene como portador líquido glicoles tales como el propilenglicol o el polietilenglicol
8. La composición de la reivindicación 1, caracterizada porque es una forma de liberación sostenida

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seleccionada a partir del grupo que incluye una inyección de depósito, preparación de implante, o bomba osmótica, los cuales se pueden formular de tal manera que permitan una liberación sostenida del ingrediente activo.

9. La composición de la reivindicación 1, caracterizada porque contiene propulsores presurizados aceptables tales como diclorodifluorometano, propano, nitrógeno y similares.
10. La composición de la reivindicación 1, caracterizada porque puede incluir vehículos tales como manteca de cacao, carboneras y polietilenglicoles, los cuales se funden a la temperatura del cuerpo, solidificando aún a temperatura de ambiente de cuarto para formas de supositorio.
11. La composición de la reivindicación 1, caracterizada porque la cantidad del natalizumab es de 1 mg/kg por paciente a 20 mg/kg por paciente para administración cada cuatro semanas durante al menos 6 meses.
12. La composición de la reivindicación 11, caracterizada porque natalizumab se encuentra presente en combinación con un compuesto que mejora la inflamación patológica.

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13. La composición de la reivindicación 12 caracterizada porque el compuesto que mejora la inflamación patológica es seleccionado del grupo que consiste de un 5-aminosalicilato, un glucocorticoide, un derivado de trioguanina, metotrexato, ciclosporina, un anticuerpo monoclonal que se une al TNF un antibiótico, un analgésico, un antidiarreico o un anticolinérgico.

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/16070 (22) International Filing Date: 31 July 1998 (31.07.98) (30) Priority Data: 08/904,423 31 July 1997 (31.07.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/904,423 (CIP) Filed on 31 July 1997 (31.07.97) (71) Applicants (for all designated States except US): ATHENA NEUROSCIENCES, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, CA 94080 (US). AMERICAN HOME PRODUCTS CORPORATION [US/US]; 5 Giraldi Farms, Madison, NJ 07940 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THORSETT, Eugene, D. [US/US]; 571 Buena Vista, Moss Beach, CA 94038 (US). SEMKO, Christopher, M. [CA/US]; 2361 Carpenter Court, Fremont, CA 94539 (US). PLEISS, Michael, A. [US/US]; 848 Stella Court, Sunnyvale, CA 94087 (US). KREFT, Anthony [US/US]; 43 Barley Court, Langhorne, PA 19047	(US). KONRADI, Andrei, W. [US/US]; 95 Cervantes #105, San Francisco, CA 94123 (US). GRANT, Francine, S. [FR/US]; 3735 Sacramento Street, San Francisco, CA 94118 (US). BAUDY, Reinhardt, Bernhard [DE/US]; 5281 Harrington Court, Doylestown, PA 18901 (US). SARANTAKIS, Dimitrios [US/US]; 262 Sentinel Avenue, Newtown, PA 18940 (US). (74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: SULFONYLATED DIPEPTIDE COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4		
(57) Abstract Disclosed are compounds which bind VLA-4. Certain of these compounds also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compounds are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compounds can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis.		

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Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*.

5 Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent

10 positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate the pharmaceutical

15 compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

20	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	30.0 8%
	Starch	305.0
25	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

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The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

15 A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
	Lactose	95

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The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

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Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
30	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
35	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
	Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

10 Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
15	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

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The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

25 Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

30	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

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The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

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Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
10	Active Ingredient	50.00mg
	Xanthan gum	4.00mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.00mg
15	Sucrose	1.75 g
	Sodium benzoate	10.00mg
	Flavor and Color	q.v.
	Purified water to	5.00ml

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The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

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Formulation Example 8

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
30	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
35	Total	425.0 mg

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This assay may also be used to determine the plasma levels needed to saturate the binding sites of other integrins, such as the $\alpha_9\beta_1$ integrin, which is the integrin most closely related $\alpha_4\beta_1$ (Palmer et al, 1993, J. Cell Bio., 123:1289). Such binding is predictive of *in vivo* utility for inflammatory conditions mediated by $\alpha_9\beta_1$ integrin, including by way of example, airway hyper-responsiveness and occlusion that occurs with chronic asthma, smooth muscle cell proliferation in atherosclerosis, vascular occlusion following angioplasty, fibrosis and glomerular scarring as a result of renal disease, aortic stenosis, hypertrophy of synovial membranes in rheumatoid arthritis, and inflammation and scarring that occur with the progression of ulcerative colitis and Crohn's disease.

Accordingly, the above-described assay may be performed with a human colon carcinoma cell line, SW 480 (ATTC #CCL228) transfected with cDNA encoding α_9 integrin (Yokosaki et al., 1994, J. Biol. Chem., 269:26691), in place of the Jurkat cells, to measure the binding of the $\alpha_9\beta_1$ integrin. As a control, SW 480 cells which express other α and β_1 subunits may be used.

Using a conventional oral formulation, compounds of this invention would be active in this model.

Example 246

In vivo Evaluation

The standard multiple sclerosis model, Experimental Autoimmune (or Allergic) Encephalomyelitis ("EAE"), was used to determine the effect of candidate compounds to reduce motor impairment in rats or guinea pigs. Reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory activity in the candidate compound. This model has been previously

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Aerosol Formulation

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

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A. Preparation of 100.0 mL of 0.5% Sodium Bicarbonate / Saline Stock Solution

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Ingredient	Gram / 100.0 mL	Final Concentration
Sodium Bicarbonate	0.5 g	0.5%
Saline	q.s. ad 100.0 mL	q.s. ad 100%

Procedure:

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1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

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B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

Ingredient	Gram / 10.0 mL	Final Concentration
Candidate Compound	0.300 g	30.0 mg/mL
0.5% Sodium Bicarbonate / Saline Stock Solution	q.s. ad 10.0 mL	q.s ad 100%

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Procedure:

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1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.
2. Add approximately 9.7 mL of 0.5% sodium bicarbonate / saline stock solution.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

Radicación No. 04-95478

**Clasificación Internacional (IPC): A61K45/00; A61K31/196; A61K31/519;
A61P1/00**

Concepto Técnico No. 3275

Patente de Invención ☒

Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒

Cap. I ☐

Cap. II ☒

No. Sol. Internacional

PCT/US03/05421

Fecha de Presentación Internal.

25-02-2003

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 93 a 243 (como se radicó inicialmente)

Reivindicaciones: Folios 244 a 257 (como se radicó inicialmente)
Folios 357 a 361 (modificación)
Folios 390 a 393 (modificación)

Dibujos: Folios 258 a 276 como se radicó inicialmente

Prioridad: Folios: 1
Fecha: 25-02-2002, País y número: US60/360,134.
Fecha: 23-04-2002, País y número: US60/360,134.

Respuesta del solicitante Folios: 371 a 375.

2. Objeto de la invención

Título de la invención: "ADMINISTRACIÓN DE AGENTES PARA EL TRATAMIENTO DE INFLAMACIÓN".

Problema Técnico Planteado: La necesidad de reducir crónicamente la inflamación patológica.

Solución: Una composición farmacéutica que contiene un inhibidor del receptor de integrina alfa 4.

IPC: A61K45/00; A61K31/196; A61K31/519; A61P1/00

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Las expresiones como "un anticuerpo monoclonal", "un estabilizador" y "un excipiente", no son concisas, abarcan una gran cantidad de materia y dan lugar a un número ilimitado de composiciones.

Las reivindicaciones 2 a 13 establecen que la composición puede contener agentes adicionales tales como adyuvantes, otros agentes inmunoestimulantes, propulsores presurizados y compuestos que mejoran la inflamación. Estos compuestos dan lugar a un número elevado de composiciones muy complejas de las cuales no se presentan ejemplos ni ensayos que soporten su utilidad.

La reivindicación 11 caracteriza la composición por la dosis que va a ser administrada al paciente y las semanas de administración. La posología con la cual se administre un medicamento a un paciente es una decisión médica y no una característica técnica de una composición.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 25-02-2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	Neurology Vol. 52(5), 23 march 1999, pp 1072-1074	A safety and pharmacokinetic study of intravenous natalizumab in patients with MS	03-1999
D2	WO9906437	Sulfonilated dipeptide compounds which inhibit leukocyte adhesion mediated by VLA-4	11-02-1999

5. Respuesta a los argumentos del solicitante:

El solicitante presenta un nuevo capítulo reivindicatorio con 13 reivindicaciones contenido en los folios 390 a 393. Luego del estudio de este documento esta oficina establece que el mismo no amplía la materia contenida en la solicitud tal y como fue presentada inicialmente y en consecuencia es aceptado para el estudio de patentabilidad.

El solicitante argumenta que los tratamientos con composiciones del arte previo para la inhibición de la inflamación, requerían de regímenes de dosificación totalmente diferentes, toda vez que la administración de dichas composiciones podían causar una reacción de respuesta del propio sistema del cuerpo, lo cual podía conducir a un reconocimiento de la inflamación como un alivio patológico y crónico resultante de la inflamación patológica.

Esta oficina no encuentra soporte en la descripción que respalde los argumentos del solicitante, la descripción carece de evidencias que permitan establecer que las composiciones del arte previo puedan causar dicha inflamación patológica. De

hecho D1 enseña que el natalizumab fue seguro y bien tolerado en un estudio con 28 pacientes con MS (pág. 4 discusión). Igualmente D1 divulga los resultados de seguridad y tolerabilidad en la página 3, en donde el más frecuente signo emergente del tratamiento fue dolor de cabeza.

El solicitante manifiesta que una persona medianamente versada en la técnica no podía lograr el perfil ventajoso de la composición en un régimen de dosis crónico.

Esta oficina no encuentra convincentes los argumentos del solicitante por cuanto D1 enseña los estudios de PK los cuales revelan que dosis entre 1.0 y 3.0 mg/kg IV de natalizumab logran un nivel sérico sostenido por 3 a 8 semanas. Lo cual sugiere que el uso de una sola dosis IV de natalizumab puede limitar las recaídas agudas de MS. Esta información claramente le indica al experto en la materia que el medicamento puede utilizarse de manera crónica gracias a su PK y a que se pueden hacer aplicaciones en periodos de tiempo prolongados. Adicionalmente el perfil de una composición para uso crónico es un resultado a alcanzar con la misma.

El solicitante argumenta que si bien D1 y D2 reportan composiciones de diversas formulas farmacéuticas, ninguna de estas anterioridades muestra una composición que contenga un estabilizador y un portador que sean útiles para las cantidades de natalizumab que se revelan en el capítulo reivindicatorio.

Esta oficina difiere de los argumentos del solicitante ya que D1 y D2 si sugieren las composiciones de la presente solicitud útiles para las cantidades de natalizumab tal y como se establece en la evaluación de nivel inventivo en el numeral 5.

El solicitante presenta dos documentos, argumentando que en ellos se establece que el natalizumab se encuentra asociado con el mejoramiento significativo en el efecto funcional más que la progresión disminuida o prevención de la discapacidad en un grupo de pacientes con MS.

Esta oficina no encuentra que estos documentos le otorguen nivel inventivo alguno a las composiciones reclamadas por cuanto las mismas ya se habían sugerido por D1 y D2 al igual que su utilidad para tratar pacientes con MS. Adicionalmente dichos documentos no establecen que los estudios realizados se hayan hecho utilizando las composiciones reclamadas en la presente solicitud, el estudio de Polman tan solo menciona que se utilizó natalizumab a una dosis de 300mg (pág 900) pero no se describe la presente formulación.

5. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La reivindicación 1 reclama "Una composición farmacéutica para tratamiento crónico de inflamación patológica en un paciente que comprende entre 0.1 a 10% de un anticuerpo monoclonal, tal como natalizumab, un estabilizador, un portador y/o un excipiente".

D1 divulga composición en viales de 5ml de 5.0 mg/ml de natalizumab (pág. 2) las cuales se diluyen en solución salina para obtener la dosis adecuada.

D2 divulga compuestos que se unen a VLA-4 para inhibir la adhesión de los leucocitos útiles en el tratamiento de enfermedades inflamatorias como el natalizumab y composiciones farmacéuticas que los contiene en las cuales el activo se puede encontrar entre el 1.2% y el 10%, que contienen agentes estabilizantes y/o portadores (abstract y ejemplos de formulación).

Análisis de las diferencias con respecto al estado de la técnica:

Características esenciales de la Solicitud	D1	D2
	Neurology	WO9906437
Una composición farmacéutica	SI (página 2 párrafo 4)	SI (273 reiv 14)
0.1 a 10 % de un anticuerpo monoclonal	NO	SI (ejemplos 1 y 3 pág 139-140)
Natalizumab	SI (pág. 2 párrafo 4)	SI (pág 235 reiv. 1)
Un estabilizador	NO	SI(pág. 136 ejemplo 2)
Un portador	NO	NO
Un excipiente	NO	SI (Pág. 137 líneas 4 a 14)

El estado de la técnica más cercano es D2 que enseña composiciones que contienen anticuerpos monoclonales como el natalizumab útiles para el tratamiento de enfermedades inflamatorias (abstract).

La solicitud se diferencia de D2 en que en la presente establece un portador. Sin embargo no se establece el tipo de portador y la utilidad o ventaja que este le da a la composición.

El Efecto Técnico que logra la diferencia es el mismo que enseña D2 que consiste en controlar la inflamación (pág 229 ejemplo 246) lo cual se demuestra mediante el modelo de esclerosis múltiple estándar. La presente solicitud enseña un ensayo de reincidencia de esclerosis múltiple (folio 185), sin embargo la descripción no establece cuál fue la composición de natalizumab utilizada y tampoco se divulga si en esta el anticuerpo se encontraba en una proporción de 0.1 a 10% y contenía algún portador, por lo tanto el rango seleccionado por el solicitante no presenta ninguna ventaja técnica frente a las composiciones conocidas; de hecho los ejemplos establecen permanentemente las dosis utilizadas las cuales son los valores realmente relevantes en una sustancia y no el porcentaje del activo en la forma farmacéutica ya que este último puede modificarse de acuerdo a las necesidades médicas mediante diluciones. La presente solicitud no contiene información que permita evidenciar una eventual ventaja de la composición con el uso del portador y de las combinaciones con otros agentes inmunoestimulantes o compuestos que mejoran la inflamación patológica que el solicitante reclama en la reivindicaciones 1, 5, 12 y 13.

El Problema Técnico Objetivo de esta solicitud es una composición farmacéutica que contiene natalizumab. Este problema ya se había resuelto con las composiciones divulgadas por D2 en las que el activo se encuentra en

proporciones del 0.5 al 10 % (ejemplos 1, 3, 8-10, la formulación de aerosol de la página 233 al 0.5%).

D1 describe una composición de natalizumab en vial de 5ml que contiene 5 mg/ml elaborada por Athena Neursciences (página 1073). Adicionalmente D1 establece el uso de dosis de 3 mg/kg de natalizumab para controlar la inflamación (abstract), la cual es también utilizada por el solicitante en los estudios resumidos en las tablas 4 a 8, en consecuencia las dosis utilizadas por el solicitante ya se habían divulgado en el estado de la técnica. Igualmente, D2 ya enseñaba que el natalizumab inhibía el tráfico de leucocitos a través de la barrera hematoencefálica revirtiendo la encefalomielitis alérgica, y da a conocer la seguridad y tolerabilidad de cinco dosis de natalizumab en pacientes MS.

Así, el objeto de la presente solicitud que consiste en una composición que contiene un anticuerpo monoclonal tal como el natalizumab, es evidente para cualquier experto en la materia a la luz de la información divulgada por D1 y D2. En consecuencia las composiciones de las reivindicaciones 1 a 13 no tienen nivel inventivo.

6. Conclusión:

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Negar** las reivindicaciones: 1 a 13 (folios: 390 a 393)

Bogotá, D.C.,

CONCEPTO TECNICO No. 3275	EXAMINADOR TECNICO Código No.202073
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REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 61106

Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO

PRIMERO: Que mediante escrito radicado en esta Superintendencia el 24 de septiembre de 2004, bajo el número 04 - 095478, entró a fase nacional la solicitud de patente de invención titulada: "ADMINISTRACION DE AGENTES PARA EL TRATAMIENTO DE INFLAMACIÓN", que corresponde a la solicitud internacional PCT/US03/05421 del 25 de febrero de 2003.

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud, y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que realizado el examen de patentabilidad se encontró que la invención no cumple con los requisitos establecidos. En consecuencia, con fundamento en lo dispuesto en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se requirió al peticionario en dos oportunidades para que se pronunciara sobre las objeciones efectuadas a la solicitud.

CUARTO: Que el solicitante mediante escritos radicados el 6 de mayo de 2008 y el 17 de julio de 2009, atendió oportunamente a los requerimientos formulados, y presentó las respectivas aclaraciones. Finalmente, allegó un nuevo capítulo reivindicatorio, el cual se ajusta a las prescripciones establecidas en el artículo 34 de la mencionada Decisión 486.

QUINTO: Que según lo dispuesto en el artículo 14 de la Decisión 486 expedida por la Comisión de la Comunidad Andina se otorgarán patentes "... para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

SEXTO: Que las reivindicaciones 1 y 13, contenidas en los folios 390 a 393, además de no ser claras ni concisas, no cumplen con el requisito de nivel inventivo, de acuerdo con las siguientes consideraciones:

1. Objeto de la invención

El objeto de la solicitud de patente de invención, según la reivindicación independiente 1, se refiere a una composición farmacéutica para tratamiento

THE FIRST PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1624 TO 1789.

THE SECOND PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1789 TO 1898.

THE THIRD PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1898 TO 1900.

THE FOURTH PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1900 TO 1901.

THE FIFTH PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1901 TO 1902.

THE SIXTH PART OF THE
BOOK IS A HISTORY OF THE
CITY OF NEW YORK FROM
1902 TO 1903.

REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 6 1106

Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

crónico de inflamación patológica en un paciente que comprende entre 0.1 a 10% de un anticuerpo monoclonal, tal como natalizumab, un estabilizador, un portador y/o un excipiente.

El problema técnico planteado es la necesidad de reducir crónicamente la inflamación patológica.

La solución a dicho problema técnico, consiste en una composición farmacéutica que contiene un inhibidor del receptor de integrina alfa 4.

2. Sobre las reivindicaciones en análisis

El artículo 30 de la Decisión 486 señala que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Al respecto ha señalado el Tribunal Andino de Justicia lo siguiente:

"...las reivindicaciones constituyen, jurídicamente hablando, el elemento de mayor importancia dentro de una solicitud de patente, pues en ellas, el examinador técnico de patentes encontrará los elementos necesarios para determinar lo que se pretende patentar, el alcance de la invención y su definición para efectos de entrar al análisis comparativo respecto del estado de la técnica. Esto es para reivindicar lo que se considera nuevo y con nivel inventivo.¹

"(...) las reivindicaciones constituyen parte esencial de la respectiva solicitud, debido a que delimitan el campo de la patente y especifican la regla técnica que se desea patentar, razones por las cuales éstas deben ser suficientemente claras y concisas. Su fundamento radica pues en la descripción respectiva, de forma tal que el alcance de la reivindicación corresponda y se justifique con el contenido de aquella". (Proceso 106-IP-2002, publicado en la G.O.A.C. N° 892, de 31 de enero de 2003, patente: BATERIA CON CONTROLADOR INCORPORADO)²

En el caso particular, pese a las modificaciones realizadas al capítulo reivindicatorio, no es claro ni conciso por las siguientes razones:

Las expresiones como "un anticuerpo monoclonal", "un estabilizador" y "un excipiente" no son concisas, pues abarcan una gran cantidad de materia y dan lugar a un amplio número de composiciones.

Las reivindicaciones 2 a 13, establecen que la composición puede contener agentes adicionales tales como adyuvantes, otros agentes inmunoestimulantes,

¹ Proceso 156-IP-2006

² Proceso 197-IP-2007

REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 6.1106
Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

propulsantes presurizados y compuestos que mejoran la inflamación. No obstante, estos compuestos dan lugar a un amplio número de composiciones complejas, de las cuales además, no se presentan ejemplos ni ensayos que soporten su utilidad.

La reivindicación 11, caracteriza la composición por la dosis que va a ser administrada al paciente y las semanas de administración. Al respecto cabe señalar, que la posología con la cual se administre un medicamento a un paciente, es una decisión médica y no una característica técnica de una composición.

Así las cosas, no obstante los requerimientos formulados oportunamente en virtud del artículo 45 de la Decisión 486, las reivindicaciones no cumplen con los requisitos de concisión y claridad exigidos por el artículo 30 de la Decisión 486.

3. Determinación del estado de la técnica

3.1. Fecha determinante para el análisis comparativo

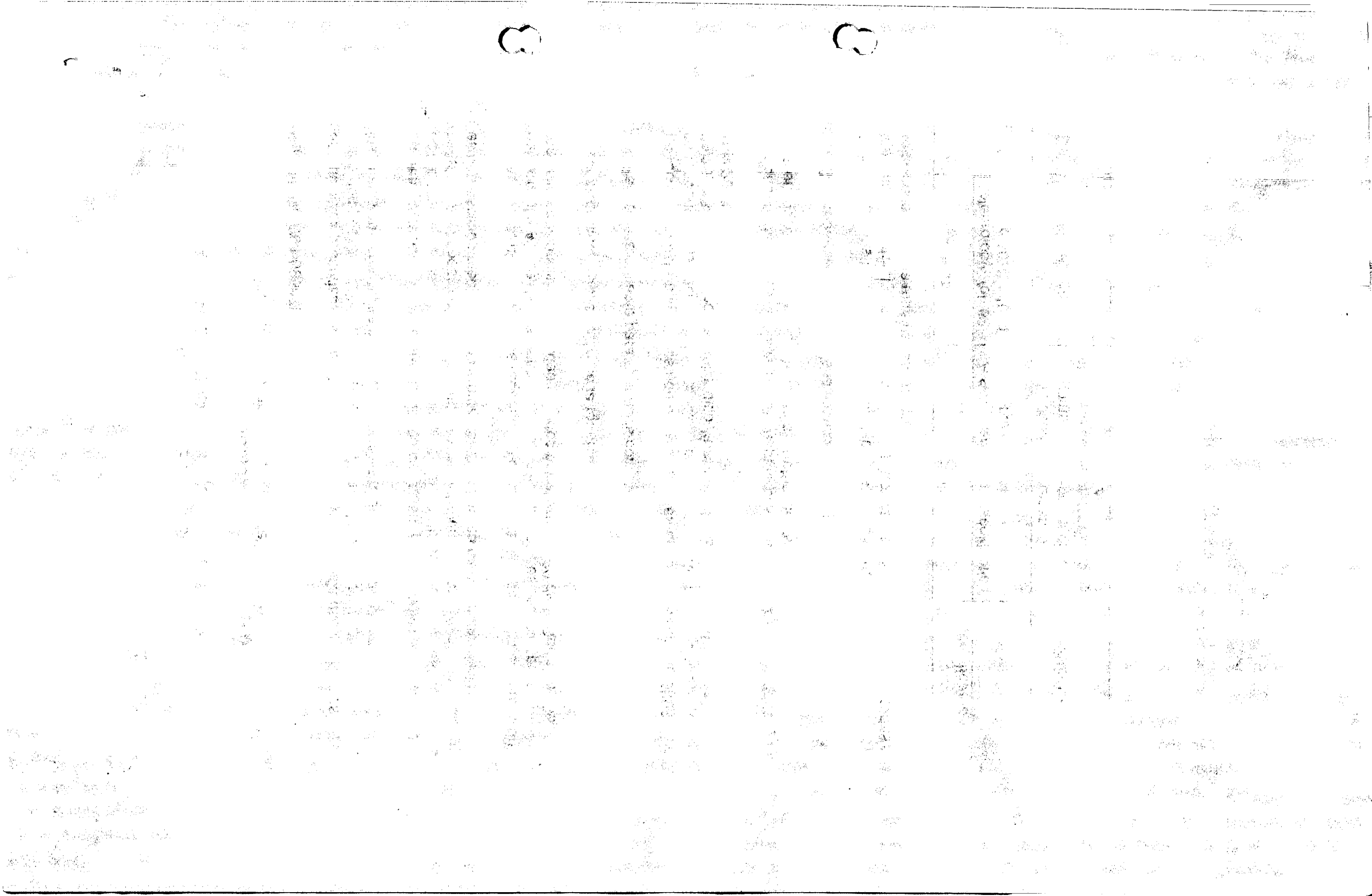
La fecha para determinar el estado de la técnica es el 25 de febrero de 2002, que corresponde a la fecha de la prioridad invocada respecto de la solicitud US No. 60/360,134. Así mismo, se reivindicó la prioridad US No. 60/374,501 del 23 de abril 2002.

Las prioridades fueron tenidas en cuenta para el examen de patentabilidad, según obra en los folios 401 y 402 del expediente eh estudio.

3.2. Documentos del estado de la técnica

Consultadas las bases de datos y los archivos con que se cuenta, se encontraron los siguientes documentos anteriores a las fechas de las prioridades invocadas y relacionados con la materia reclamada:

No.	Documento	Título	Fecha de publicación
D1	Neurology Vol. 52 (5), pp 1072 - 1074	A safety and pharmacokinetic study of intravenous natalizumab in patients with MS	1999-03-23
D2	WO 9906437	Sulfonilated dipeptide compounds which inhibit leukocyte adhesion mediated by VLC-4	1999-02-11



REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 611061
Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

4. Nivel inventivo

Según lo dispuesto en el artículo 18 de la Decisión 486, "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."

El estado de la técnica, al tenor de lo dispuesto en el artículo 16 de la misma Decisión, comprende "...todo lo que haya sido accesible al público, por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".

El Tribunal de Justicia de la Comunidad Andina ha dicho sobre este requisito, lo siguiente:

El nivel inventivo, implica que la invención presente "...un salto cualitativo en relación con la técnica existente. Este requerimiento es desarrollado por el artículo 4 de la Decisión 344 (hoy artículo 18 D. 486) que presupone el requisito de nivel inventivo al establecer que la invención goza de dicho nivel al no derivar de manera evidente del estado de la técnica, ni resultar obvia para una persona entendida o versada en la materia.

"Este requisito ofrece al examinador la posibilidad de determinar si con los conocimientos técnicos que existían al momento de la invención, se hubiese podido llegar de manera evidente a la misma, o si el resultado hubiese sido obvio para un experto medio en la materia de que se trate, es decir, para una persona del oficio y normalmente versada en la materia técnica correspondiente."

(...)

"En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado.

"Este Tribunal, al respecto, manifiesta que: *'el inventor debe reunir los méritos que le permitan atribuirse una patente, sólo si la invención fruto de su investigación y desarrollo creativo constituye "un salto cualitativo en la elaboración de la regla técnica", actividad intelectual mínima que permitirá que su invención no sea evidente (no obvia) del estado de la técnica. Es decir, que con el requisito del nivel inventivo, lo que se pretende es dotar al examinador técnico de un elemento que le permita afirmar o no si a la invención objeto de estudio no se habría podido llegar a partir de los conocimientos técnicos que existían en ese momento dentro del estado de la técnica (...)' (Proceso 13-IP-2004)*³.

³ Proceso 105-IP-2008

[The page contains extremely faint, illegible text, likely bleed-through from the reverse side. The text is organized into several paragraphs and possibly a table or list structure, but the characters are too light to transcribe accurately.]

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REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 61106
Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

En el presente caso, el objeto carece de nivel inventivo, porque a los ojos de un experto medio en la materia, el problema técnico que pretendía resolver la solicitud, se solucionaría con la aplicación del conocimiento brindado por el estado de la técnica.

En efecto, la reivindicación 1 reclama "Una composición farmacéutica para tratamiento crónico de inflamación patológica en un paciente que comprende entre 0.1 a 10% de un anticuerpo monoclonal, tal como natulizumab, un estabilizador, un portador y/o un excipiente".

Por su parte, la anterioridad D1 divulga una composición en viales de 5 ml de 5.0 mg/ml de natulizumab (página 2), las cuales se diluyen en solución salina para obtener la dosis adecuada.

Adicionalmente, la anterioridad D2 divulga compuestos que se unen a VLA-4 para inhibir la adhesión de los leucocitos útiles en el tratamiento de enfermedades inflamatorias como el natalizumab y composiciones farmacéuticas que los contiene, en las cuales el activo se puede encontrar entre el 1.2% y el 10%, que contienen agentes estabilizantes y/o portadores (abstract y ejemplos de formulación).

A continuación, se presenta una tabla que refleja las diferencias de las características esenciales de la solicitud, con respecto al estado de la técnica:

Características esenciales de la solicitud	D1	D2
	Neurology	WO 9906437
Una composición farmacéutica	Si (página 2, párrafo 4)	Si (273 reiv. 14)
0.1 a 10% de un anticuerpo monoclonal	No	Si (ejemplos 1 y 3, pág. 139, 140)
Natalizumab	Si (pág. 2, párrafo 4)	Si (pág. 235, reiv. 1)
Un estabilizador	No	Si (pág. 136, ej. 2)
Un portador	No	No
Un excipiente	No	Si (pág. 137, líneas 4 a 14)

Como se observa, el estado de la técnica más cercano es D2, que enseña composiciones que contienen anticuerpos monoclonales como el natulizumab, útiles para el tratamiento de enfermedades inflamatorias (abstract).

La solicitud se diferencia de D2, en que en esta se establece un portador. Sin embargo, no se establece el tipo de portador y la utilidad o ventaja que este le da a la composición.

Además, el efecto técnico que logra la diferencia es el mismo que enseña D2, que

1990年 12月 25日
 1991年 1月 1日

10-10-1964

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

1. The first step in the process is to identify the problem. This involves gathering information about the situation and understanding the needs of the stakeholders involved.

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1. The first step in the process of the investigation is the identification of the problem. This is done by the investigator who is responsible for the study. The next step is to collect data. This is done by the investigator who is responsible for the study. The next step is to analyze the data. This is done by the investigator who is responsible for the study. The next step is to interpret the results. This is done by the investigator who is responsible for the study. The next step is to draw conclusions. This is done by the investigator who is responsible for the study. The next step is to report the findings. This is done by the investigator who is responsible for the study. The next step is to discuss the implications. This is done by the investigator who is responsible for the study. The next step is to write the report. This is done by the investigator who is responsible for the study. The next step is to publish the report. This is done by the investigator who is responsible for the study. The next step is to disseminate the findings. This is done by the investigator who is responsible for the study. The next step is to evaluate the process. This is done by the investigator who is responsible for the study. The next step is to improve the process. This is done by the investigator who is responsible for the study. The next step is to repeat the process. This is done by the investigator who is responsible for the study. The next step is to end the process. This is done by the investigator who is responsible for the study.

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1. The first part of the document is a list of names and their corresponding dates. The names are: "John Doe", "Jane Smith", "Bob Johnson", "Alice Brown", "Charlie White", "David Green", "Eve Black", "Frank Gray", "Grace Pink", "Henry Blue", "Ivy Yellow", "Jack Purple", "Karen Red", "Leo Orange", "Mia Silver", "Noah Gold", "Olivia Bronze", "Peter Copper", "Quinn Iron", "Rory Steel", "Sam Tin", "Tina Lead", "Uma Zinc", "Victor Nickel", "Wendy Platinum", "Xavier Silver", "Yara Gold", "Zoe Bronze", "Adam Copper", "Eve Iron", "Frank Steel", "Grace Tin", "Henry Lead", "Ivy Zinc", "Jack Nickel", "Karen Platinum", "Leo Silver", "Mia Gold", "Noah Bronze", "Olivia Copper", "Peter Iron", "Quinn Steel", "Rory Tin", "Tina Lead", "Uma Zinc", "Victor Nickel", "Wendy Platinum", "Xavier Silver", "Yara Gold", "Zoe Bronze". The dates are: "1990-01-01", "1990-02-01", "1990-03-01", "1990-04-01", "1990-05-01", "1990-06-01", "1990-07-01", "1990-08-01", "1990-09-01", "1990-10-01", "1990-11-01", "1990-12-01", "1991-01-01", "1991-02-01", "1991-03-01", "1991-04-01", "1991-05-01", "1991-06-01", "1991-07-01", "1991-08-01", "1991-09-01", "1991-10-01", "1991-11-01", "1991-12-01", "1992-01-01", "1992-02-01", "1992-03-01", "1992-04-01", "1992-05-01", "1992-06-01", "1992-07-01", "1992-08-01", "1992-09-01", "1992-10-01", "1992-11-01", "1992-12-01", "1993-01-01", "1993-02-01", "1993-03-01", "1993-04-01", "1993-05-01", "1993-06-01", "1993-07-01", "1993-08-01", "1993-09-01", "1993-10-01", "1993-11-01", "1993-12-01", "1994-01-01", "1994-02-01", "1994-03-01", "1994-04-01", "1994-05-01", "1994-06-01", "1994-07-01", "1994-08-01", "1994-09-01", "1994-10-01", "1994-11-01", "1994-12-01", "1995-01-01", "1995-02-01", "1995-03-01", "1995-04-01", "1995-05-01", "1995-06-01", "1995-07-01", "1995-08-01", "1995-09-01", "1995-10-01", "1995-11-01", "1995-12-01", "1996-01-01", "1996-02-01", "1996-03-01", "1996-04-01", "1996-05-01", "1996-06-01", "1996-07-01", "1996-08-01", "1996-09-01", "1996-10-01", "1996-11-01", "1996-12-01", "1997-01-01", "1997-02-01", "1997-03-01", "1997-04-01", "1997-05-01", "1997-06-01", "1997-07-01", "1997-08-01", "1997-09-01", "1997-10-01", "1997-11-01", "1997-12-01", "1998-01-01", "1998-02-01", "1998-03-01", "1998-04-01", "1998-05-01", "1998-06-01", "1998-07-01", "1998-08-01", "1998-09-01", "1998-10-01", "1998-11-01", "1998-12-01", "1999-01-01", "1999-02-01", "1999-03-01", "1999-04-01", "1999-05-01", "1999-06-01", "1999-07-01", "1999-08-01", "1999-09-01", "1999-10-01", "1999-11-01", "1999-12-01", "2000-01-01", "2000-02-01", "2000-03-01", "2000-04-01", "2000-05-01", "2000-06-01", "2000-07-01", "2000-08-01", "2000-09-01", "2000-10-01", "2000-11-01", "2000-12-01", "2001-01-01", "2001-02-01", "2001-03-01", "2001-04-01", "2001-05-01", "2001-06-01", "2001-07-01", "2001-08-01", "2001-09-01", "2001-10-01", "2001-11-01", "2001-12-01", "2002-01-01", "2002-02-01", "2002-03-01", "2002-04-01", "2002-05-01", "2002-06-01", "2002-07-01", "2002-08-01", "2002-09-01", "2002-10-01", "2002-11-01", "2002-12-01", "2003-01-01", "2003-02-01", "2003-03-01", "2003-04-01", "2003-05-01", "2003-06-01", "2003-07-01", "2003-08-01", "2003-09-01", "2003-10-01", "2003-11-01", "2003-12-01", "2004-01-01", "2004-02-01", "2004-03-01", "2004-04-01", "2004-05-01", "2004-06-01", "2004-07-01", "2004-08-01", "2004-09-01", "2004-10-01", "2004-11-01", "2004-12-01", "2005-01-01", "2005-02-01", "2005-03-01", "2005-04-01", "2005-05-01", "2005-06-01", "2005-07-01", "2005-08-01", "2005-09-01", "2005-10-01", "2005-11-01", "2005-12-01", "2006-01-01", "2006-02-01", "2006-03-01", "2006-04-01", "2006-05-01", "2006-06-01", "2006-07-01", "2006-08-01", "2006-09-01", "2006-10-01", "2006-11-01", "2006-12-01", "2007-01-01", "2007-02-01", "2007-03-01", "2007-04-01", "2007-05-01", "2007-06-01", "2007-07-01", "2007-08-01", "2007-09-01", "2007-10-01", "2007-11-01", "2007-12-01", "2008-01-01", "2008-02-01", "2008-03-01", "2008-04-01", "2008-05-01", "2008-06-01", "2008-07-01", "2008-08-01", "2008-09-01", "2008-10-01", "2008-11-01", "2008-12-01", "2009-01-01", "2009-02-01", "2009-03-01", "2009-04-01", "2009-05-01", "2009-06-01", "2009-07-01", "2009-08-01", "2009-09-01", "2009-10-01", "2009-11-01", "2009-12-01", "2010-01-01", "2010-02-01", "2010-03-01", "2010-04-01", "2010-05-01", "2010-06-01", "2010-07-01", "2010-08-01", "2010-09-01", "2010-10-01", "2010-11-01", "2010-12-01", "2011-01-01", "2011-02-01", "2011-03-01", "2011-04-01", "2011-05-01", "2011-06-01", "2011-07-01", "2011-08-01", "2011-09-01", "2011-10-01", "2011-11-01", "2011-12-01", "2012-01-01", "2012-02-01", "2012-03-01", "2012-04-01", "2012-05-01", "2012-06-01", "2012-07-01", "2012-08-01", "2012-09-01", "2012-10-01", "2012-11-01", "2012-12-01", "2013-01-01", "2013-02-01", "2013-03-01", "2013-04-01", "2013-05-01", "2013-06-01", "2013-07-01", "2013-08-01", "2013-09-01", "2013-10-01", "2013-11-01", "2013-12-01", "2014-01-01", "2014-02-01", "2014-03-01", "2014-04-01", "2014-05-01", "2014-06-01", "2014-07-01", "2014-08-01", "2014-09-01", "2014-10-01", "2014-11-01", "2014-12-01", "2015-01-01", "2015-02-01", "2015-03-01", "2015-04-01", "2015-05-01", "2015-06-01", "2015-07-01", "2015-08-01", "2015-09-01", "2015-10-01", "2015-11-01", "2015-12-01", "2016-01-01", "2016-02-01", "2016-03-01", "2016-04-01", "2016-05-01", "2016-06-01", "2016-07-01", "2016-08-

REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 6 1 1 0 6

Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

consiste en controlar la inflamación (página 229, ejemplo 246), lo cual se demuestra mediante el modelo de esclerosis múltiples estándar. La presente solicitud enseña un ensayo de reincidencia de esclerosis múltiple (folio 185), sin embargo la descripción no establece cuál fue la composición de natalizumab utilizada y tampoco divulga si en esta el anticuerpo se encontraba en una proporción de 0.1 a 10% y contenía algún portador, por lo tanto el rango seleccionado por el solicitante no presenta ninguna ventaja técnica frente a las composiciones conocidas; de hecho, los ejemplos establecen permanentemente las dosis utilizadas, las cuales son los valores realmente relevantes en una sustancia y no el porcentaje del activo en la forma farmacéutica, ya que este último puede modificarse de acuerdo a las necesidades médicas mediante diluciones. De tal suerte, la presente solicitud no contiene información que permita evidenciar una eventual ventaja de la composición con el uso del portador y de las combinaciones con otros agentes inmunoestimulantes o compuestos que mejoran la inflamación patológica, que el solicitante reclama en las reivindicaciones 1, 5, 12 y 13.

Es decir, el problema técnico objetivo de esta solicitud, es una composición farmacéutica que contiene natalizumab. Pero, este problema ya se había resuelto con las composiciones divulgadas por D2, en las que el activo se encuentra en proporción del 0.5 al 10% (ejemplos 1, 3, 8-10, la formulación de aerosol de la página 233 al 0.5%).

Ahora bien, D1 describe una composición de natalizumab en vial de 5 ml que contiene 5 mg/ml elaborada por Athena Neursciences (página 1073). Adicionalmente, D1 establece el uso de dosis de 3 mg/kg de natalizumab para controlar la inflamación (abstract), la cual es también utilizada por el solicitante en los estudios resumidos en las tablas 4 a 8, de tal manera que las dosis utilizadas por el solicitante ya se habían divulgado en el estado de la técnica. Igualmente, D2 ya enseñaba que el natalizumab inhibía el tráfico de leucocitos a través de la barrera hematoencefálica revirtiendo la encefalomiелitis alérgica, y da a conocer la seguridad y tolerabilidad de cinco dosis de natalizumab en pacientes MS.

Así, el objeto de la presente solicitud que consiste en una composición que contiene un anticuerpo monoclonal tal como el natalizumab, es evidente para cualquier experto en la materia a la luz de la información divulgada por D1 y D2.

En consecuencia, las composiciones de las reivindicaciones 1 a 13 no tienen nivel inventivo, razón por la cual la solicitud no cumple con lo dispuesto en el artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 6.1106
Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

5. Sobre la respuesta del solicitante

Argumenta el solicitante, que los tratamientos con composiciones del arte previo para la inhibición de la inflamación requerían de regímenes de dosificación totalmente diferentes, toda vez que la administración de dichas composiciones podían causar una reacción de respuesta del propio sistema del cuerpo, lo cual podía conducir a un reconocimiento de la inflamación como un alivio patológico y crónico resultante de la inflamación patológica.

Al respecto cabe señalar, que no se encuentra soporte en la descripción que respalde los argumentos del solicitante. La descripción carece de evidencias que permitan establecer que las composiciones del arte previo puedan causar dicha inflamación patológica. De hecho D1 enseña que el natalizumab fue seguro y bien tolerado en un estudio con 28 pacientes con MS (página 4). Igualmente D1 divulga los resultados de seguridad y tolerabilidad (página 3), en donde el más frecuente signo emergente del tratamiento fue dolor de cabeza.

Manifiesta el solicitante, que una persona medianamente versada en la materia técnica no podía lograr el perfil ventajoso de la composición en un régimen de dosis crónico.

A este argumento, es preciso responder que D1 enseña los estudios de PK, los cuales revelan que dosis entre 1.0 y 3.0 mg/kg IV de natalizumab logran un nivel sérico sostenido por 3 a 8 semanas. Lo cual, sugiere que el uso de una sola dosis IV de natalizumab puede limitar las recaídas agudas de MS. Esta información claramente le indica a una persona normalmente versada en la materia, que el medicamento puede utilizarse de manera crónica gracias a su PK y que se pueden hacer aplicaciones en periodos de tiempo prolongados. Adicionalmente, el perfil de una composición para uso crónico es un resultado a alcanzar con la misma.

El solicitante argumenta, que si bien D1 y D2 reportan composiciones de diversas formulas farmacéuticas, ninguna de estas anterioridades muestra una composición que contenga un estabilizador y un portador que sean útiles para las cantidades de natalizumab que se revelan en el capítulo reivindicatorio.

Al respecto, D1 y D2 sí sugieren las composiciones de la presente solicitud útiles para las cantidades de natalizumab, tal y como se establece en numeral anterior, correspondiente al análisis de nivel inventivo de la solicitud.

Finalmente, el solicitante presenta dos documentos y argumenta que en ellos se establece que el natalizumab se encuentra asociado con el mejoramiento significativo en el efecto funcional más que la progresión disminuida o prevención de la discapacidad en un grupo de pacientes con MS.

TO THE HONORABLE
MEMBERS OF THE
LEGISLATIVE ASSEMBLY
OF THE PROVINCE OF ONTARIO
IN PARLIAMENT ASSEMBLED
AT TORONTO
JANUARY 1908

THE REPORT OF THE
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REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN N° 6.11.06

Por la cual se niega una patente de invención

Rad. N° PCT/04-095478

Cabe señalar, que dichos documentos no son relevantes para el análisis de patentabilidad, debido a que las composiciones reclamadas ya se habían sugerido por D1 y D2, al igual que su utilidad para tratar pacientes con MS. Adicionalmente, dichos documentos no establecen que los estudios realizados se hayan hecho utilizando las composiciones reclamadas en la presente solicitud y, como se advierte, el estudio de Polman tan solo menciona que se utilizó natalizumab a una dosis de 300 mg (pág. 900) pero no se describe la presente formulación.

Por lo expuesto, se concluye que no obstante los comentarios formulados por el solicitante, la solicitud no cumple lo dispuesto en el artículo 18 de la Decisión 486.

RESUELVE

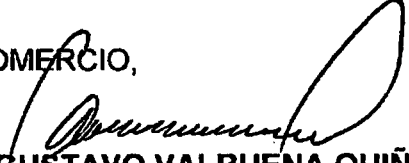
ARTICULO PRIMERO: Negar el privilegio de patente de invención a la creación denominada: "ADMINISTRACION DE AGENTES PARA EL TRATAMIENTO DE INFLAMACIÓN".

ARTICULO SEGUNDO: Notificar personalmente a la doctora Dilia Rodríguez D'Aleman, en su calidad de apoderada de la sociedad ELAN PHARMACEUTICALS, INC., o a quien haga sus veces, el contenido de la presente resolución, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio al momento de notificarse o dentro de los 5 días hábiles siguientes.

NOTIFIQUESE Y CUMPLASE

Dada en Bogotá D.C., a los **30 NOV. 2009**.

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctora
DILIA RODRIGUEZ D'ALEMAN
Carrera 11 No. 86 – 53. Piso 6.
Bogotá D.C.

202067

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DETALLE DE NOTIFICACION DE PROVIDENCIA**

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COMO CONTINUAR
LA CONSULTA**RESOLUCION 61106 de fecha 30/11/2009**

Establece Notificar a: RODRIGUEZ D'ALEMAN DILIA MARIA
Con notificación directamente a: RODRIGUEZ D'ALEMAN DILIA MARIA
Vinculación del Notificado al Asunto : APODERADO
Presentó Recurso : SI en Fecha 30/12/2009
Notificación : POR LISTADO ≈ Listado No. : 214, Consecutivo No. 27678 del Año 2009 • NOTIFICAR
Fechas del Edicto (dd/mm/aaaa) : FIJADO el: 10/12/2009 y DESFIJADO el 23/12/2009
Fecha de Notificación : 23/12/2009 (dd/mm/aaaa)
Forma de Comunicar la Notificación : LOCAL
Fecha V/miento Notificación Personal: 09/12/2009 (dd/mm/aaaa)
Fecha de Ejecutoria Individual :
Despacho Comisorio:
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Estado de Correspondencia: ENVIADO , de fecha 2009-12-01 08:00:00



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