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THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 28, 2022

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *12/766,173*
FILING DATE: *April 23, 2010*
PATENT NUMBER: *8377903*
ISSUE DATE: *February 19, 2013*

Certified by

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

April 23, 2010

CLAIM OF PRIORITY UNDER 35 USC §119
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Docket No.	:	SER.125D1
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified patent application hereby reaffirms their claim to the right of priority granted pursuant to 35 USC §119 based upon European Application No. 04106909.7, filed December 22, 2004.

A certified copy of the above European application can be found in the parent application, U.S. application Serial No. 11/722,018. Applicants respectfully request that the certified copy of the foreign priority application be made of record in the subject application pursuant to MPEP 201.14(b).

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb

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April 23, 2010

INFORMATION DISCLOSURE
STATEMENT
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Docket No.	:	SER.125D1
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

In accordance with 37 CFR §1.97 and §1.98, Applicants would like to bring to the attention of the Examiner, the references cited in the following patent application:
U.S. Serial No. 11/722,018, which entered the U.S. national stage on June 18, 2007, from international application No. PCT/EP2005/056954, filed December 20, 2005.

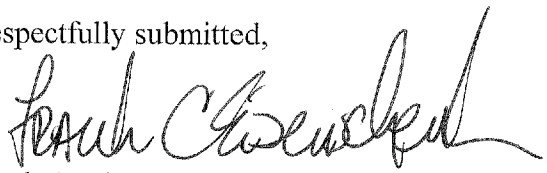
The subject application claims the benefit under 35 USC §120 of the filing date of patent application Serial No. 11/722,018. Applicants respectfully request that the references cited in the Information Disclosure Statement submitted in the 11/722,018 application, as well as any references cited by the Patent Office during the prosecution thereof, be made of record in the subject application. As copies of the references made of record in the 11/722,018 application, and cited on the attached form PTO/SB/08, can be found in the 11/722,018 casefile, copies of those references are not provided herewith.

J:\SER\125D1\PTO-Misc\IDS.doc/DNB/jb

It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

Applicants respectfully assert that the substantive provisions of 37 CFR §§1.97 and 1.98 are met by the foregoing statements.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb
Attachment: Form PTO/SB/08

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	3

Complete if Known	
Application Number	
Filing Date	April 23, 2010
First Named Inventor	Giampiero De Luca
Art Unit	
Examiner Name	
Attorney Docket Number	SER.125D1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-4,964,848	10-23-1990	Bloom	All
	U2	US-5,506,214	04-09-1996	Beutler	All
	U3	US-2010/0021429	01-28-2010	Brentzel *et al.*	All
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO 04/087101 A2	10/14/2004	Ivax Corporation	All	
	F2	EP 0 626 853 B1	04/26/200	The Scripps Research Institute	All	
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	
Filing Date	April 23, 2010
First Named Inventor	Giampiero De Luca
Group Art Unit	
Examiner Name	
Attorney Docket Number	SER.125D1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R1	BEUTLER, E. *et al.* "Marrow Suppression Produced by Repeated Doses of Cladribine", *Acta Haematol*, 1994, pp. 10-15, Vol. 91.	
	R2	BEUTLER, E. *et al.* "Treatment of Multiple Sclerosis and Other Autoimmune Diseases With Cladribine", *Seminars in Hematology*, January 1, 1996, pp. 45-52, Vol. 33, No. 1, Supplement 1.	
	R3	BEUTLER, E. *et al.* "The treatment of chronic progressive multiple sclerosis with cladribine", *Proc. Natl. Acad. Sci. USA*, February 1996, pp. 1716-1720, Vol. 93.	
	R4	ELLISON, G. *et al.* "Oral Cladribine for Multiple Sclerosis", *Neurology*, March 1997, P03.070, pp. A174-A175, Vol. 48, No. 3, XP008047069.	
	R5	GRIEB, P. *et al.* "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients", *Archivum Immunologiae et Therapiae Experimentalis*, 1995, pp. 323-327, Vol. 43, No. 5-6.	
	R6	KAZIMIERCZUK, Z. *et al.* "Synthesis of 2'-Deoxytubercidin, 2'-Deoxyadenosine, and Related 2'-Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure", *J. Am. Chem. Soc.*, 1984, pp. 6379-6382, Vol. 106, No. 21.	
	R7	KURTZKE, J. "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)", *Neurology*, November 1983, pp. 1444-1452, Vol. 33.	
	R8	LANGTRY, H. *et al.* "Cladribine: A Review of its Use in Multiple Sclerosis", *Biodrugs*, May 1998, pp. 419-433, Vol. 9, No. 3.	
	R9	LASSMANN, H. *et al.* "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy", *TRENDS in Molecular Medicine*, March 2001, pp. 115-121, Vol. 7, No. 3.	
	R10	LUBLIN, F. *et al.* "Defining the clinical course of multiple sclerosis: Results of an international survey", *Neurology*, April 1996, pp. 907-911, Vol. 46.	
	R11	LUCCHINETTI, C. *et al.* "Multiple sclerosis: recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment", *Current Opinion in Neurology*, 2001, pp. 259-269, Vol. 14.	
	R12	MATTSON, D. "Update on the diagnosis of multiple sclerosis", *Expert Review of Neurotherapeutics*, May 2002, pp. 319-327, Vol. 2, No. 3.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	
				Filing Date	April 23, 2010
				First Named Inventor	Giampiero De Luca
(use as many sheets as necessary)				Group Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	SER.125D1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R13	MCDONALD, W. *et al.* "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidlines from the International Panel on the Diagnosis of Multiple Sclerosis", *Annals of Neurology*, July 2001, pp. 121-127, Vol. 50, No. 1.	
	R14	MILLER, R. *et al.* "Therapeutic advances in ALS", *Neurology*, 1996, pp. S217, Vol. 47, Suppl. 4.	
	R15	NOSEWORTHY, J. *et al.* "Multiple Sclerosis", *The New England Journal of Medicine*, September 28, 2000, pp. 938-952, Vol. 343, No. 13.	
	R16	POSER, C. *et al.* "New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols", *Annals of Neurology*, March 1983, pp. 227-231, Vol. 13, No. 3.	
	R17	RICE, G. *et al.* "Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial", *Neurology*, March 2000, pp. 1145-1155, Vol. 54.	
	R18	ROMINE, J. *et al.* "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis", *Proceedings of the Association of American Physicians*, *January*/February 1999, pp. 35-44, Vol. 111, No. 1.	
	R19	SCHUMACHER, G. *et al.* "Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis", *Annals New York Academy of Sciences*, March 31, 1965, pp. 552-568, Vol. 122.	
	R20	SELBY, R. *et al.* "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis", *Can. J. Neurol. Sci.*, 1998, pp. 295-299, Vol. 25.	
	R21	SIPE, J. *et al.* "A neurologic rating scale (NRS) for use in multiple sclerosis", *Neurology*, October 1984, pp. 1368-1372, Vol. 34.	
	R22	STELMASIAK, Z. *et al.* "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis", *Med. Sci Monit.*, 1998, pp. 4-8, Vol. 4, No. 1.	
	R23		
	R24		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Attorney Docket Number:	SER.125D1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	9	52	468
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1558**

Electronic Acknowledgement Receipt

EFS ID:	7476036
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	23-APR-2010
Filing Date:	
Time Stamp:	14:02:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1558
RAM confirmation Number	271
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	executed-Dec-POA.pdf	1226254 d3dc201e3e69a976177f6b2ee3b0300478e774ea	no	8
Warnings:					
Information:					
2	Application Data Sheet	ADS.pdf	177233 df861bbdfb1bfdf540e391b42e196598ab6ad25e	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3		as-filed.pdf	2518006 dcf85330afeeffa49f4116e5dccb02b77f549810	yes	31

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	25
Claims	26	30
Abstract	31	31

Warnings:					
Information:					
4	Request for USPTO to retrieve priority docs	COP.pdf	61544 5251f42b81ac54492d6c14f5c33a2e2ec4ba6208	no	1
Warnings:					
Information:					
5		IDS.pdf	673900 b5eac3a5ca339072a9a2d03e99cc15b682b02eb3	yes	5

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Transmittal Letter	1	2

	Information Disclosure Statement (IDS) Filed (SB/08)		3	5	
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	36384 25a2c4f108ceeccc23fc7b8dbaa956b63c485577	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4693321		

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

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

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

PTO/SB/01A (09-04)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☑ Application No. PCT/EP2005/056954, filed on DECEMBER 20, 2005,

☑ as amended on JUNE 18, 2007 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

PTO/SB/01A (09-04)
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FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

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PTO/SB/01A (09-04)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

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This declaration is directed to:

☐ The attached application, or

☑ Application No. PCT/EP2005/056954, filed on DECEMBER 20, 2005,

☑ as amended on JUNE 18, 2007 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

PTO/SB/81 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Cladribine Regimen for Treating ...
Art Unit	
Examiner Name	
Attorney Docket Number	SER-125

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 23557

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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I am the:

☑ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	12/07/2007
Name	GIAMPIERO DE LUCA	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Cladribine Regimen for...
Art Unit	1614
Examiner Name	
Attorney Docket Number	SER.125

I hereby revoke all previous powers of attorney given in the above-identified application.

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☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

23557

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I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	15th July 2009
Name	ARNAUD YTHIER	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	Alain Munafo	Date	July 7, 2009
Name	ALAIN MUNAFO	Telephone	+ 41 22 414 3833
Title and Company	Merck Serono S.A. Geneva		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	11-March-2010
Name	MARIA LOPEZ-BRESNAHAN	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

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Application Information

Application Type::	Regular (Continuation)
Subject Matter::	Utility
Suggested Classification::	None
Suggested Group Art Unit::	None
CD-ROM or CD-R?::	None
Number of CD disks::	None
Number of copies of CDs::	None
Sequence submission?::	No
Computer Readable Form?::	No
Number of Copies of CRF::	None
Title::	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
Attorney Docket Number::	SER.125D1
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	None
Total Drawing Sheets::	None
Small Entity?::	No
Petition included?::	No
Petition Type::	N/A
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	INVENTOR
Primary Citizenship Country::	ITALY
Status::	UNKNOWN
Inventor One Given Name::	GIAMPIERO
Family Name::	DE LUCA
City of Residence::	CONCHES/GENEVA
Country of Residence::	SWITZERLAND
Street of Mailing Address::	CHEMIN DES CONCHES 15B
City of Mailing Address::	CONCHES/GENEVA
Country of Mailing Address::	SWITZERLAND
Postal or Zip Code of Mailing Address::	CH-1231

Applicant Information

Applicant Authority Type::	INVENTOR
Primary Citizenship Country::	CH AND FR
Status::	UNKNOWN
Inventor Two Given Name::	ARNAUD
Family Name::	YTHIER
City of Residence::	COLLEX-BOSSY
Country of Residence::	SWITZERLAND
Street of Mailing Address::	ROUTE DE VIRELOUP 88
City of Mailing Address::	COLLEX-BOSSY
Country of Mailing Address::	SWITZERLAND
Postal or Zip Code of Mailing Address::	1239

Applicant Information

Applicant Authority Type::	INVENTOR
Primary Citizenship Country::	CH
Status::	UNKNOWN
Inventor Three Given Name::	ALAIN
Family Name::	MUNAFO
City of Residence::	TARTEGNIN
Country of Residence::	SWITZERLAND
Street of Mailing Address::	RUE DES PRESSOIRS 6
City of Mailing Address::	TARTEGNIN
Country of Mailing Address::	SWITZERLAND
Postal or Zip Code of Mailing Address::	1180

Applicant Information

Applicant Authority Type::	INVENTOR
Primary Citizenship Country::	US
Status::	UNKNOWN
Inventor Four Given Name::	MARIA
Family Name::	LOPEZ-BRESNAHAN
City of Residence::	LINCOLN
State or Province of Residence::	MA
Street of Mailing Address::	145 SOUTH GREAT ROAD
City of Mailing Address::	LINCOLN
State or Province of mailing address::	MA
Postal or Zip Code of Mailing Address::	01773

Representative Information

Representative Customer Number::	000023557

Correspondence Information

Correspondence Customer Number::	000023557
Telephone Number One::	(352) 375-8100
Telephone Number Two::	
Fax Number::	(352) 372-5800
Electronic Mail Address::	fce@slspatents.com

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	Continuation of	11/722,018	June 18, 2007
11/722,018 is the	National Stage of	PCT/EP2005/056954	December 20, 2005
PCT/EP2005/056954	An application claiming the benefit under 35 USC 119(e) of	60/638,669	December 22, 2004

Foreign Priority Information

Country::	Application Number::	Filing Date::	Priority Claimed::
EP	04106909.7	December 22, 2004	Yes

Assignee Information

Assignee Name::	MERCK SERONO S.A.
Street of Mailing Address::	CENTRE INDUSTRIEL
City of Mailing Address::	COINSINS, VAUDE
Country of Mailing Address::	SWITZERLAND
Postal or Zip Code of Mailing Address::	1267

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Serial No. 11/722,018, filed June 18, 2007, which is the U.S. national stage application of International Patent Application No. PCT/EP2005/056954, filed December 20, 2005, which claims the benefit of U.S. Provisional Patent Application No. 60/638,669, filed December 22, 2004, the disclosures of which are hereby incorporated by reference in their entireties, including all figures, tables and amino acid or nucleic acid sequences.

FIELD OF THE INVENTION

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

BACKGROUND OF THE INVENTION

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (*Lublin and Reingold above).* 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (*Noseworthy et al., The New England Journal of Medicine, 2000, 343, 13, 938-952*). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (*Mc Donald et al., 2001, Ann. Neurol., 50:121-127*).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (*EP 626853B1 and US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice at al., 2000, Neurology, 54, 5, 1145-1155).* In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (*Beutler et al., 1996, Proc. Nat. Acad. Sci. USA, 93, 1716-1720; Romine et al., 1999 above).* Phase III study results, were positive on the significant reduction of MRI-measured brain lesions (*Rice at al., 2000, above*).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (*Selby et al., 1998, above; Beutler et al., 1994, Acta hematol., 91:10-15*). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c.

administration. As a result, *Beutler et al. (Beutler et al., 1996, Seminars in Hematology, 33, 1(S1), 45-52*) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Grieb et al. reported a small trial in 11 patients with remitting-relapsing multiple sclerosis (*Grieb et al., 1995, Archivum Immunologiae et Therapiae Experimentalis, 43 (5-6), 323-327*) wherein Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4-5.7 mg/kg (patients of about 52 and about 75 kilos, respectively) i.e. a total effective dose of 2-2.85 mg/kg. For some patients, a single re-treatment of 5 days was performed at a cumulative dose of 0.4-0.66 mg/kg after a cladribine free-period of 3 or 6 months. The side effects observed with the regimen above were said to be less severe than the ones observed in the study on patients suffering from chronic progressive multiple sclerosis treated by i.v. infusion of Cladribine (*Sipe et al., 1994, Lancet, 344, 9-13*) but were still present. In addition, the therapeutic efficacy of the oral regimen above versus the i.v. infusion therapy was questioned (*Grieb et al., 1995, above*) and a group of "non-responders" has been identified (*Stelmasiak et al., 1998, Laboratory Investigations, 4(1), 4-8*).

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of Cladribine treatment between the treatment periods is also desirable.

SUMMARY OF THE INVENTION

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding

the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg or the total dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days is 1.7 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg or the total effective dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 0.7 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments.

Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of **(i)** an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and **(ii)** a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months

or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months, typically at least of about 8 months.

A "Maintenance Treatment" consists in the sequential succession of **(i)** a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and **(ii)** a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria *(Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31).*

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau,

in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 1444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379.* Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before

use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.

IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.

Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free periods (ii) and/or (iv) last between about 8 and about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period (iii) is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period (iii) is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the maintenance period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period and wherein the pharmaceutical formulation is a pharmaceutical formulation described in WO 2004/087101 or in WO 2004/087100.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

n a preferred embodiment, the invention provides a method of treating multiple sclerosis with Cladribine, wherein Cladribine is orally administered following the sequential steps below:

(i) Administering Cladribine, such that the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) Administering no Cladribine during a Cladribine free period;

(iii) Administering Cladribine such that the total dose of Cladribine reached at the end of a maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) And optionally, a Cladribine-free period wherein no Cladribine is administered.

In a further preferred embodiment, the invention provides a method wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

In a further preferred embodiment, the invention provides a method wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the maintenance period is followed by a Cladribine-free period.

In another further embodiment, the invention provides a method according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 3 to about 30 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 10 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is orally administered about 1 to about 7 days per month during the induction period.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) are repeated at least one or two times.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be administered in combination with interferon-beta.

EXAMPLES

The following abbreviations refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra-veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **2-CdA** (2-chloro-2'deoxyadenosine or Cladribine), **UI** (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

EXAMPLE 1: ORAL CLADRIBINE IN THE TREATMENT OF RELAPSING FORMS OF MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

Table 1:

Group	2-CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2-CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2-CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

Table 2

Name of ingredients	**Formula mg/tablet**	**Formula mg/tablet**
Cladribine-2-hydroxypropyl-ß-cyclodextrin- complex*	153.75 equivalent to 10 mg 2-CdA	30.60 equivalent to 3 mg 2-CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl-ß-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

Table 3							
Patient weight ranges (kg)			**Total target dose (kg) equivalent to 1.75 mg/kg**		**Number of pills (10 mg)/induction period**		
Min	**Mid range**	**Max**	**Min**	**Max**	**Month 1**	**Month 2**	**Total**
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 4									
Patient weight ranges (kg)			**Total target dose (kg) equivalent to 3.5 mg/kg**		**Number of pills (10 mg)/induction period**				
Min	**Mid range**	**Max**	**Min**	**Max**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Total**
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailablility of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailablility of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above*; *Sipe et al., 1984, above*; and *Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.

The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2-CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

CLAIMS

We claim:

1. A method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i);

(iv) a cladribine-free period wherein no cladribine is administered.

2. The method according to claim 1, wherein the induction period lasts about 4 months.

3. The method according to claim 1, wherein the induction period lasts about 2 months.

4. The method according to claim 1, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

5. The method according to claim 1, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

6. The method according to claim 1, wherein the cladribine-free period (ii) lasts about 10 months.

7. The method according to claim 1, wherein the cladribine-free (iv) period lasts 10 months.

8. The method according to claim 1, wherein the maintenance period lasts about 2 months.

9. The method according to claim 1, wherein the formulation is orally administered following the sequential steps below:

(i) an induction period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period wherein no cladribine is administered;

(iii) a maintenance period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine is administered;

wherein the maintenance period (iii) lasts about 2 months; the cladribine-free period (iv) lasts about 10 months; the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeatedly performed one, two or three times.

10. The method according to claim 1, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

11. The method according to claim 1, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

12. The method according to claim 1, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

13. The method according to claim 1, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

14. The method according to claim 1, wherein the steps (iii) to (iv) are repeated at least one time.

15. The method according to claim 1, wherein the steps (iii) to (iv) are repeated at least two times.

16. The method according to claim 1, wherein the formulation is administered in combination with interferon-beta.

17. A method of treating relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis comprising the oral administration of a formulation comprising cladribine to an individual having relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg; and

(iv) a cladribine-free period wherein no cladribine is administered.

18. The method according to claim 17, wherein the induction period lasts about 4 months.

19. The method according to claim 17, wherein the induction period lasts about 2 months.

20. The method according to claim 17, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

21. The method according to claim 17, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

22. The method according to claim 17, wherein the cladribine-free period (ii) lasts about 10 months.

23. The method according to claim 17, wherein the cladribine-free (iv) period lasts 10 months.

24. The method according to claim 17, wherein the maintenance period lasts about 2 months.

25. The method according to claim 17, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

26. The method according to claim 17, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

27. The method according to claim 17, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

28. The method according to claim 17, wherein the steps (iii) to (iv) are repeated at least one or two times.

29. The method according to claim 17, wherein the formulation is administered in combination with interferon-beta.

ABSTRACT OF THE INVENTION

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be the orally administered and wherein re-treatments are possible.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/766,173	04/23/2010	1614	1558	SER.125D1	29	2

CONFIRMATION NO. 1906

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

FILING RECEIPT

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Date Mailed: 05/04/2010

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

Applicant(s)

Giampiero De Luca, Conches/Geneva, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

Assignment For Published Patent Application

Merck Serono S.A., Coinsins, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 23557

Domestic Priority data as claimed by applicant

This application is a CON of 11/722,018 06/18/2007 PAT 7,713,947
which is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 04/29/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/766,173**

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Early Publication Request: No

Title

Cladribine Regimen for Treating Multiple Sclerosis

Preliminary Class

514

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CONFIRMATION NO. 1906

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

POA ACCEPTANCE LETTER

OC000000041376590

Date Mailed: 05/04/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/23/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/ybedada/

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

04106909.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 04106909.7
Demande no:

Anmeldetag:
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Anmelder/Applicant(s)/Demandeur(s):

Applied Research Systems ARS Holding N.V.
Pietermaai 15
Curacao
ANTILLES NEERLANDAISES

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Cladribine regimen for treating Multiple Sclerosis

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
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Cladribine regimen for treating Multiple Sclerosis

Field of the Invention

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

Background of the Invention

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (*Lublin and Reingold above).* 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (*Noseworthy et al., The New England Journal of Medicine, 2000, 343, 13, 938-952*). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (*Mc Donald et al., 2001, Ann. Neurol., 50:121-127*).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (*EP 626853B1 and US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice at al., 2000, Neurology, 54, 5, 1145-1155).* In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (*Beutler et al., 1996, Proc. Nat. Acad. Sci. USA, 93, 1716-1720; Romine et al., 1999 above)*. Phase III study results, were positive on the significant reduction of MRI-measured brain lesions (*Rice at al., 2000, above*).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (*Selby et al., 1998, above; Beutler et al., 1994, Acta hematol., 91:10-15*). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c. administration. As a result, *Beutler et al. (Beutler et al., 1996, Seminars in Hematology, 33, 1(S1), 45-52*) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible.

Summary of the Invention

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting

multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i).

Detailed Description of the invention

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments.

Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of **(i)** an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and **(ii)** a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months.

A "Maintenance Treatment" consists in the sequential succession of **(i)** a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and **(ii)** a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria *(Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31).*

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the

presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium -enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 14444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the

contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379*. Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers

include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.
IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.
Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be

administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

Examples

The following abbreviations refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra -veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **UI** (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1: Oral cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

Table 1:

Group	2CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

Table 2:

Name of ingredients	**Formula mg/tablet**	**Formula mg/tablet**
Cladribine-2-hydroxypropyl-ß-cyclodextrin- complex*	153.75 equivalent to 10 mg 2CdA	30.60 equivalent to 3 mg 2CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl-ß-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

Table 3:

Patient weight ranges (kg)			**Total target dose (kg) equivalent to 1.75 mg/kg**		**Number of pills (10 mg)/induction period**		
Min	**Mid range**	**Max**	**Min**	**Max**	**Month 1**	**Month 2**	**Total**
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid range	Max	Min	Max	Month 1	Month 2	Total
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 4:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	**Mid range**	**Max**	**Min**	**Max**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Total**
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailablility of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailablility of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above*; *Sipe et al., 1984, above*; and *Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.
The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

Claims:

1. Use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:
   (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
   (ii) A Cladribine-free period wherein no Cladribine is administered;
   (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);
   (iv) A Cladribine-free period wherein no Cladribine is administered.

2. Use according to claim 1 wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

3. Use according to claims 1 or 2 wherein the induction period lasts up to about 2 months.

4. Use according to any of the preceding claims wherein the induction period lasts up to about 4 months.

5. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

6. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

7. Use according to any of the preceding claims wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

8. Use according to any of the preceding claims wherein the Cladribine-free (iv) period lasts up to about 10 months.

9. Use according to any of the preceding claims wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

10. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

11. Use according to claim 1 wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 8 months or up to about 10 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total

dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

12. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine.

13. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 10 mg Cladribine.

14. Use according to any of the preceding claims wherein the pharmaceutical formulation is orally administered about 1 to about 7 days per month during the induction period.

15. Use according to any of the preceding claims wherein the steps (iii) to (iv) are repeated at least one or two times.

16. Use according to any of the preceding claims wherein wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

Abstract of the invention:

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be the orally administered and wherein re-treatments are possible.

To: euspto@slspatents.com,,
From: PAIR_eOfficeAction@uspto.gov
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May 04, 2010 05:54:42 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	APP.FILE.REC	05/04/2010	SER.125D1
	N570	05/04/2010	SER.125D1

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Date: 04/23/10

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/766,173

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	29 minus 20 =	9	x$26		OR	x$52	468
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1558

APPLICATION AS AMENDED – PART II

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

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

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

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

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1

CONFIRMATION NO. 1906

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

PUBLICATION NOTICE

OC00000043020367

Title: Cladribine Regimen for Treating Multiple Sclerosis

Publication No.US-2010-0203017-A1
Publication Date:08/12/2010

NOTICE OF PUBLICATION OF APPLICATION

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

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Aug 13, 2010 05:42:37 AM

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	NTC.PUB	08/12/2010	SER.125D1

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PLUS Search Results for S/N 12766173, Searched Fri Dec 09 08:40:43 EST 2011

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7713947 99
20090081163 99
20100021429 99
20100203017 99
5716946 85
20100260755 85
6455553 83
20100196318 83
6194395 69
6291504 69
6407103 69
6372719 61
7037900 61
7173016 61
7727968 61
7993638 61
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

23557 7590 12/19/2011

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
12/19/2011	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	12/766,173	DE LUCA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *23 April 2010*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *1-29* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-29* is/are rejected.

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☒ All b)☐ Some * c)☐ None of:

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

2.☒ Certified copies of the priority documents have been received in Application No. 11/722,018.

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/23/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. Claims **1-29** are pending and under examination in the current office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted April 23, 2010 has been considered and the references therein are of record.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 12/722,018, filed on June 18, 2007.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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

5. Claims 1-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 7,713,947. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass the therapeutic oral administration of cladribine for the treatment of multiple sclerosis. Both the claims of the '947 patent and the instant application recite the same method steps (i.e., (i) an induction period, (ii) a cladribine-free period, (iii) a maintenance period, and (iv) a cladribine-free period) comprising the same dosages and length of treatment administration and/or abstinence from treatment. The patented claims also recite that the formulation may be administered in combination with interferon-beta. Hence, the patented claims directed to a method of treating patients having multiple sclerosis (MS) would render obvious the instantly recited methods of treating relapsing-remitting MS or early secondary progressive MS, which would be encompassed by the treatment of MS in general.

6. Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-71 and 79 of copending Application No. 12/301,083. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims are

encompass the therapeutic administration of cladribine in combination with interferon beta for the treatment of patients suffering from multiple sclerosis (MS), including progressive MS or relapsing-remitting MS (see, for example, claim 79 of the '083 application). Additionally, both the present claims and the claims of the '083 application recite the same or similar doses of cladribine to be administered and/or reached at the end of the treatment phases, as well as the same sequential steps of the therapeutic method (i.e., induction phase, cladribine-free period, maintenance phase, cladribine-free period) and time periods for each. Accordingly, the claims of the '083 application render obvious the presently recited invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

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

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

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2004/087101 A2 by Bodor et al. (listed on IDS) and Grieb et al. (*Arch Immunol Therap Exp.* 1995; 43:323-327; listed on IDS) in view of US Patent 4,964,848 to Bloom (listed on IDS).

The teachings of Bodor et al. and Grieb et al. are cumulative. Both references teach the use of cladribine administered orally for the treatment of patients having multiple sclerosis (MS). Specifically, Bodor et al. disclose the administration of a therapeutically effective amount of cladribine via oral administration for the treatment of MS, wherein 10 mg of cladribine is administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment (see p. 23, lines 7-20). Here, because Bodor states "10 months of no treatment", it is implied that following these 10 months, treatment with cladribine is resumed. Hence, Bodor teaches an “induction

period" of treatment that is about 2 months followed by a cladribine-free period of about 10 months, wherein it is implied that treatment may begin again following the non-treatment period, which is on point to limitations within claims 1, 3, 6, 9, 17, 19 and 22 reciting an treatment method comprising an induction period and a cladribine-free period. Also, Bodor discloses that the daily dose of cladribine administered is 10 mg, which addresses present claims 11, 12, 25 and 26 (i.e., the formulation is administered at a daily dose of 3 to 30 mg cladribine; a daily dose of 10 mg cladribine). This dose is taught to be administered for 5-7 days per month, which meets the limitation of claims 13 and 27 (i.e., the formulation is orally administered 1 to 7 days per month during the induction period). Thus, for 7 days of treatment each month for 2 months, and for an average adult human weighing approximately 65 kg, the total dose of cladribine reached at the end of this period would be 2.15 mg/kg (i.e., (2 x (10 mg x 7)) / 65 kg), which is within the range of about 1.7 mg/kg to about 3.5 mg/kg as in base claims 1 and 17. However, it is clear that the total dose reached at the end of the initial treatment period is dependent upon the number of days cladribine is being administered per month (i.e., 5 to 7) and the weight of the patient being administered the treatment. For example, a woman weighing approximately 58 kg and treated for 2 months with 10 mg cladribine daily for 5 days per month would reach a total dose of 1.72 mg/kg, which would be on point to claims 4 and 20 (i.e., the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg).

Further, Bodor teaches that one of skill in the art will appreciate that the therapeutically effective amount of cladribine administered may be lowered or increased

by fine tuning and/or by administering cladribine with another active ingredient (see p. 24, lines 1-4). For example, cladribine may be administered with one or more additional active ingredients for the treatment of MS, such as the co-administration of cladribine with interferon-beta (see p. 24, lines 10-18), which addresses present claims 16 and 29 regarding the combined use of cladribine with interferon-beta.

Consistent with the teachings of Bodor, Grieb et al. teach the treatment of patients having relapsing-remitting MS comprising the oral administration of cladribine. Grieb discloses that cladribine was administered orally at 10 mg for 5 consecutive days, as 6 monthly courses followed by one or two additional courses at 3, 6 or 9 month intervals (see abstract and p. 324). In other words, Grieb teaches a treatment method comprising an initial treatment period of up to 6 months, followed by a non-treatment period of about 9 months, followed by another treatment cycle of about 6 months and non-treatment period of about 9 months, which treatment cycle could be repeated again. These teachings are on point to the presently recited (i) “induction period”, (ii) "cladribine-free" period of about 8 to 10 months, (iii) "maintenance period", and (iv) “cladribine-free” period of claims 1, 9 and 17. The treatment was effective to provide a progressive reduction in lymphocytes to around 1000/μl on average (see abstract). Grieb also notes that the treatments were well tolerated, and with this dosing and schedule, cladribine seems relatively safe in MS patients (see abstract).

Taken together, the combined teachings of Bodor et al. and Grieb et al. provide for a method of treating MS, including relapsing-remitting MS, comprising the oral administration of cladribine, wherein a treatment course comprises an initial treatment

period of 2 to 6 months (which encompasses the instant 2 to 4 months) comprising the daily administration of cladribine for 5-7 days each month, followed by a non-treatment period (i.e., cladribine-free period) lasting 3 to 10 months (encompassing the instant 8 to 10 months), followed by another treatment period (i.e., a maintenance phase) of 2 to 6 months in which cladribine is administered for 5-7 days each month, followed again by another non-treatment period of 3 to 10 months. The treatment (i.e., maintenance) / non-treatment periods may be repeated once more according to Grieb and implied by Bodor. According to the combined teachings, it would therefore be possible to arrive at a final total dose of about 3.5 mg/kg at the end of the induction period if, for example, 10 mg cladribine is administered daily for 5 days each month for 4 months to a woman weighing about 58 kg (i.e., [4 x (10 mg x 5)] / 58 kg = 3.45 mg/kg, which is about 3.5 mg/kg). As such, the ranges provided by the combined Bodor and Grieb references encompass the recited cladribine doses and dosing schedules of the present claims.

The difference, therefore, is that neither of the above references teach that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase.

Bloom discusses the treatment of MS and other autoimmune diseases, wherein effective treatment requires an intense induction phase during which time lymphocytes are continuously depleted from circulation to a level of less than 500 cells/μl, followed by a maintenance phase in a lower intensity treatment regimen to hold the overall blood lymphocyte count to less than 500 cells/μl (see columns 3-4). While the initial induction phase of treatment is accomplished in the Bloom reference by lymphoctapheresis and

the maintenance phase of treatment is accomplished with the use of an immunosuppressive/immunomodulatory drug other than cladribine, the principle of Bloom's teachings remains the same: effective treatment of MS requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down. Even with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4 lines 39-49 regarding the use of azathioprine (AZA) and prednisone).

Thus, based upon the teachings of Bloom, the ordinarily skilled artisan would have recognized that effective treatment of MS involves the removal of the majority of activated lymphocytes from the patient in an initial treatment phase, followed by a maintenance phase in which the numbers of lymphocytes are maintained a reduced level. The person of ordinary skill would have also been aware that cladribine is useful in treating MS because it is an immunosuppressive agent that functions by reducing the numbers of activated lymphocytes (and in particular, monocytes, which are presumably activated against self-antigens). Particularly in view of the chronic nature of multiple sclerosis, in order to reduce the severity or duration of future relapses (or to prevent them altogether) the artisan would have been aware that long-term treatment success would require a therapy that is sustainable and well-tolerated by the patient.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat multiple sclerosis with oral cladribine according to a cyclic treatment regimen, wherein treatment involves an intense induction phase

followed by a maintenance phase, and wherein the total dosage administered in the maintenance phase is less than the total dosage administered in the induction phase. Additionally, even though cladribine therapy is taught as being generally well-tolerated with a low incidence of adverse effects (see Bodor reference), in order to reduce the overall treatment costs associated with cladribine therapy and further lessen the risk of adverse side effects, the artisan would have been motivated to use a lower dose in subsequent treatment periods (i.e., the maintenance phase) that is still sufficient to sustain a therapeutically-effective immunosuppressive state. This idea is also presented in the teachings of Bloom, which suggest that subsequent rounds of treatment with an immunomodulatory agent should be at a lower overall dose(s) than the initial treatment with the agent. The artisan would have had a reasonable expectation that such a method comprising the oral administration of cladribine would be successful in the treatment of MS based upon the demonstrated effectiveness in reducing activated lymphocytes reported by Grieb and the general knowledge in the art with respect to the use of cladribine for treating MS (see, for example US Patent 5,506,214 to Beutler, listed on IDS).

Further, a particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the treatment durations, frequency of treatment (i.e., time between active therapy periods), and administered dosages are clearly recognized result-effective

variables that a person of ordinary skill in the art would routinely optimize (see MPEP § 2144.05). In fact, the disclosure of Bodor explicitly states that it is within the skill of the ordinary artisan to adjust or fine-tune (either by increasing or decreasing) the administered dose of cladribine to achieve a therapeutically effective amount. The same could also be said with respect to adjusting the duration of active treatment (i.e, 2 to 4 months), the time between active treatment periods (i.e., 8 to 10 months), and how many times the treatment cycle may need to be repeated (i.e., one or two times). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal treatment schedule and cladribine dosage for MS therapy. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of treatment schedules and dosages would have been obvious at the time of Applicants' invention.

Conclusion

9. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

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

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/Kimberly A Ballard/
Examiner, Art Unit 1649

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	106	De-luca-g$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 10:58
L2	15	ythier-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 10:59
L3	6	munafo-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:01
L4	6	lopez-bresnahan-m$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:01
L11	358	merck-serono-$.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:02
L13	23	l11 and (2cda cladribine 2-chlorodeoxyadenosine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:04
L14	8664	2cda cladribine 2-chlorodeoxyadenosine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:06
L15	2709	l14 and (multiple adj sclerosis)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:07
L16	58	l14 same2 (("1.5" "1.6." "1.7" "1.8" "1.9" "2.0" 2 "2.1" "2.2" "2.3" "2.4"	US-PGPUB; USPAT;	OR	OFF	2011/12/09 11:13

		"2.5" "2.6" "2.7" "2.8" "2.9" "3.0" "3.1" "3.2" "3.3" "3.4" "3.5" "3.6" "3.7" "3.8" "3.9" 4 "4.0") with mg/kg)	USOCR; FPRS; EPO; JPO; DERWENT			
L17	2550	l15 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:14
L18	55	l16 and oral$	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:14
L19	2627	l15 and oral$	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/12/09 11:32
L20	181505	(dosing regimen administration) same (intermittent course period cycle)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:33
L21	1990	l19 and l20	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:34
L22	42780	l20 same (months weeks)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:34
L23	958	l22 and l19	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:34
L24	565388	(combination combined adjunct) with (therapy treatment agent therapeutic)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:36
L25	993	l24 same ("ifn.beta" interferon-beta (interfereon near beta))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/12/09 11:37
L26	44	l25 and l23	US-PGPUB; USPAT;	OR	ON	2011/12/09 11:37

			USOCR; FPRS; EPO; JPO; DERWENT			

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	25	De-luca-g$.in.	USPAT; UPAD	OR	OFF	2011/12/09 11:01
L6	3	ythier-a$.in.	USPAT; UPAD	OR	OFF	2011/12/09 11:01
L7	1	munafo-a$.in.	USPAT; UPAD	OR	OFF	2011/12/09 11:02
L8	1	lopez-bresnahan-m$.in.	USPAT; UPAD	OR	OFF	2011/12/09 11:02
L12	65	merck-serono-$.as.	USPAT; UPAD	OR	OFF	2011/12/09 11:03

12/9/2011 11:43:05 AM
C:\Users\kballard\Documents\EAST\Workspaces\12.766173.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12766173	DE LUCA ET AL.
	Examiner	Art Unit
	KIMBERLY A BALLARD	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (PALM, EAST, NPL)	12/09/2011	KAB
EAST (USPAT, USOCR, USPGPUB, DERWENT, EPO, JPO, FPRS)	12/09/2011	KAB
STN (MEDLINE, BIOSIS, CAPLUS, EMBASE)	12/09/2011	KAB
PLUS search	12/09/2011	STIC

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
	Inventor & Assignee search - see EAST search	12/09/2011	KAB

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	
Filing Date	April 23, 2010
First Named Inventor	Giampiero De Luca
Art Unit	
Examiner Name	
Attorney Docket Number	SER.125D1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-4,964,848	10-23-1990	Bloom	All
	U2	US-5,506,214	04-09-1996	Beutler	All
	U3	US-2010/0021429	01-28-2010	Brentzel *et al.*	All
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	F1	WO 04/087101 A2	10/14/2004	Ivax Corporation	All	
	F2	EP 0 626 853 B1	04/26/200	The Scripps Research Institute	All	
	F3					
	F4					
	F5					
	F6					
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 3

Complete if Known	
Application Number	
Filing Date	April 23, 2010
First Named Inventor	Giampiero De Luca
Group Art Unit	
Examiner Name	
Attorney Docket Number	SER.125D1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	R1	BEUTLER, E. *et al.* "Marrow Suppression Produced by Repeated Doses of Cladribine", *Acta Haematol*, 1994, pp. 10-15, Vol. 91.	
	R2	BEUTLER, E. *et al.* "Treatment of Multiple Sclerosis and Other Autoimmune Diseases With Cladribine", *Seminars in Hematology*, January 1, 1996, pp. 45-52, Vol. 33, No. 1, Supplement 1.	
	R3	BEUTLER, E. *et al.* "The treatment of chronic progressive multiple sclerosis with cladribine", *Proc. Natl. Acad. Sci. USA*, February 1996, pp. 1716-1720, Vol. 93.	
	R4	ELLISON, G. *et al.* "Oral Cladribine for Multiple Sclerosis", *Neurology*, March 1997, P03.070, pp. A174-A175, Vol. 48, No. 3, XP008047069.	
	R5	GRIEB, P. *et al.* "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients", *Archivum Immunologiae et Therapiae Experimentalis*, 1995, pp. 323-327, Vol. 43, No. 5-6.	
	R6	KAZIMIERCZUK, Z. *et al.* "Synthesis of 2'-Deoxytubercidin, 2'-Deoxyadenosine, and Related 2'-Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure", *J. Am. Chem. Soc.*, 1984, pp. 6379-6382, Vol. 106, No. 21.	
	R7	KURTZKE, J. "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)", *Neurology*, November 1983, pp. 1444-1452, Vol. 33.	
	R8	LANGTRY, H. *et al.* "Cladribine: A Review of its Use in Multiple Sclerosis", *Biodrugs*, May 1998, pp. 419-433, Vol. 9, No. 3.	
	R9	LASSMANN, H. *et al.* "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy", *TRENDS in Molecular Medicine*, March 2001, pp. 115-121, Vol. 7, No. 3.	
	R10	LUBLIN, F. *et al.* "Defining the clinical course of multiple sclerosis: Results of an international survey", *Neurology*, April 1996, pp. 907-911, Vol. 46.	
	R11	LUCCHINETTI, C. *et al.* "Multiple sclerosis: recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment", *Current Opinion in Neurology*, 2001, pp. 259-269, Vol. 14.	
	R12	MATTSON, D. "Update on the diagnosis of multiple sclerosis", *Expert Review of Neurotherapeutics*, May 2002, pp. 319-327, Vol. 2, No. 3.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 3

Complete if Known	
Application Number	
Filing Date	April 23, 2010
First Named Inventor	Giampiero De Luca
Group Art Unit	
Examiner Name	
Attorney Docket Number	SER.125D1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R13	MCDONALD, W. *et al.* "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidlines from the International Panel on the Diagnosis of Multiple Sclerosis", *Annals of Neurology*, July 2001, pp. 121-127, Vol. 50, No. 1.	
	R14	MILLER, R. *et al.* "Therapeutic advances in ALS", *Neurology*, 1996, pp. S217, Vol. 47, Suppl. 4.	
	R15	NOSEWORTHY, J. *et al.* "Multiple Sclerosis", *The New England Journal of Medicine*, September 28, 2000, pp. 938-952, Vol. 343, No. 13.	
	R16	POSER, C. *et al.* "New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols", *Annals of Neurology*, March 1983, pp. 227-231, Vol. 13, No. 3.	
	R17	RICE, G. *et al.* "Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial", *Neurology*, March 2000, pp. 1145-1155, Vol. 54.	
	R18	ROMINE, J. *et al.* "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis", *Proceedings of the Association of American Physicians*, *January*/February 1999, pp. 35-44, Vol. 111, No. 1.	
	R19	SCHUMACHER, G. *et al.* "Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis", *Annals New York Academy of Sciences*, March 31, 1965, pp. 552-568, Vol. 122.	
	R20	SELBY, R. *et al.* "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis", *Can. J. Neurol. Sci.*, 1998, pp. 295-299, Vol. 25.	
	R21	SIPE, J. *et al.* "A neurologic rating scale (NRS) for use in multiple sclerosis", *Neurology*, October 1984, pp. 1368-1372, Vol. 34.	
	R22	STELMASIAK, Z. *et al.* "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis", *Med. Sci Monit.*, 1998, pp. 4-8, Vol. 4, No. 1.	
	R23		
	R24		

Examiner Signature	/Kimberly Ballard/	Date Considered	12/09/2011

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APPLICANTS

Giampiero De Luca, Conches/Geneva, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

**** CONTINUING DATA ***************************

This application is a CON of 11/722,018 06/18/2007 PAT 7,713,947
which is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

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Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/KIMBERLY BALLARD/ Examiner's Signature	☐ Initials	SWITZERLAND	0	29	2

ADDRESS

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

TITLE

Cladribine Regimen for Treating Multiple Sclerosis

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L1              1 S E3

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     FILE 'REGISTRY' ENTERED AT 13:13:45 ON 09 DEC 2011
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     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 13:14:33 ON 09 DEC 2011
L3           8821 S L2
L4           2253 S DE LUCA G?/AU
L5              2 S L4 AND L3
L6              2 DUP REM L5 (0 DUPLICATES REMOVED)
L7              3 S L4 AND (CLADRIBINE OR 2-CDA OR 2-CHLORODEOXYADENOSINE OR 2-C
L8              3 DUP REM L7 (0 DUPLICATES REMOVED)
L9            167 S YTHIER A?/AU
L10        184510 S MULTIPLE SCLEROSIS
L11             9 S L9 AND L10
L12             3 DUP REM L11 (6 DUPLICATES REMOVED)
L13           217 S MUNAFO A?/AU
L14             7 S L13 AND L10
L15             4 DUP REM L14 (3 DUPLICATES REMOVED)
L16            50 S LOPEZ-BRESNAHAN M?/AU
L17            30 S L16 AND L10
L18            13 DUP REM L17 (17 DUPLICATES REMOVED)
L19          9898 S L2 OR CLADRIBINE OR 2-CDA OR 2-CHLORODEOXYADENOSINE OR 2-CHLO
L20          1058 S L19 AND L10
L21            51 S L20 AND ((TREATMENT OR THERAP? OR REGIME OR ADMINIST?)(P)(MON
L22            21 DUP REM L21 (30 DUPLICATES REMOVED)
L23         52994 S INTERFERON-BETA OR (BETA(A)INTERFERON) OR INTERFERON-B O
L24           465 S L20 AND L23
L25           664 S L19(P)ORAL?
L26           173 S L24 AND L25
L27       1052026 S (COMBIN? OR ADJUNCT)(S)(TREATMENT OR THERAP? OR ADMINIST? OR
L28            14 S L26 AND L27
L29            11 DUP REM L28 (3 DUPLICATES REMOVED)
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To: euspto@slepatents.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23557

Dec 19, 2011 05:26:43 AM

Dear PAIR Customer:

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	CTNF	12/19/2011	SER.125D1
	1449	12/19/2011	SER.125D1

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Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Serial No.	:	12/766,173
Filed	:	April 23, 2010
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action dated December 19, 2011, please amend the above-identified patent application as follows:

In the Specification

Please substitute the following paragraph on page 9, beginning at line 5:

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, ~~polyvinyl~~ polyvinyl alcohol in water, etc. with a typical sugar coating.

Please substitute the following paragraph on page 9, beginning at line 15:

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose,~~ maizestarch~~ maize starch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl ~~sulfate)~~sulfate. Tablets may be coated according to methods well known in the art.

Please substitute the following paragraph on page 15, beginning at line 26:

In another embodiment, the invention provides a ~~a useuse~~ of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

Please substitute the following paragraphs on page 24, beginning at line 1:

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2-CdA cyclodextrin formulation such ~~as~~ that the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a ~~bioavailablility~~bioavailability of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2-CdA cyclodextrin formulation such ~~as~~ that the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a ~~bioavailablility~~bioavailability of about 40%); followed by 8 months of no treatment.

Remarks

Claims 1-29 are pending in the subject application and are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants note that the Office Action Summary indicates that the Examiner objects to the specification. However, no objections have been set forth in the Office Action. Applicants respectfully request clarification of the objection and the identification of those portions of the specification to which any objection exists.

Claims 1-29 are rejected under the doctrine of obviousness-type double patenting over claims 1-48 of U.S. Patent No. 7,713,947 and claims 1-29 are provisionally rejected for obviousness-type double patenting over claims 42-71 and 79 of co-pending application 12/301,083. Applicants acknowledge that a Terminal Disclaimer can be filed to overcome this rejection and respectfully request that this issue be held in abeyance until such time as allowable subject matter is identified.

Claims 1-29 are rejected under 35 U.S.C. § 103(a) as obvious over Bodor *et al.* (WO 2004/087101 and Grieb *et al.* (1995) in view of Bloom (U.S. Patent 4,964,848). The Office Action indicates that the Bodor *et al.* and Grieb *et al.* references teach the use of cladribine administered orally for the treatment of patients having multiple sclerosis (MS) and are cumulative in nature. The Office Action states:

> Specifically, Bodor *et al.* disclose the administration of a therapeutically effective amount of cladribine via oral administration for the treatment of MS, wherein 10 mg of cladribine is administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Here, because Bodor states "10 months of no treatment", it is implied that following these 10 months, treatment with cladribine is resumed. Hence, Bodor teaches an "induction period" of treatment that is about 2 months followed by a cladribine-free period of about 10 months, wherein it is implied that treatment may begin again following the nontreatment period, which is on point to limitations within claims 1, 3, 6, 9, 17, 19 and 22 reciting a treatment method comprising an induction period and a cladribine-free period. Also, Bodor discloses that the daily dose of cladribine administered is 10 mg, which addresses present claims 11, 12, 25 and 26 (i.e., the formulation is administered at a daily dose of 3 to 30 mg cladribine; a daily dose of 10 mg cladribine). This dose is taught to be administered for 5-7 days per month, which meets the limitation of claims 13 and 27 (i.e., the formulation is orally administered 1 to 7 days per month during the induction period). Thus, for

> 7 days of treatment each month for 2 months, and for an average adult human weighing approximately 65 kg, the total dose of cladribine reached at the end of this period would be 2.15 mg/kg (i.e., (2 x (10 mg x 7)) / 65 kg), which is within the range of about 1.7 mg/kg to about 3.5 mg/kg as in base claims 1 and 17. However, it is clear that the total dose reached at the end of the initial treatment period is dependent upon the number of days cladribine is being administered per month (i.e., 5 to 7) and the weight of the patient being administered the treatment. For example, a woman weighing approximately 58 kg and treated for 2 months with 10 mg cladribine daily for 5 days per month would reach a total dose of 1.72 mg/kg, which would be on point to claims 4 and 20 (i.e., the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg).
>
> Further, Bodor teaches that one of skill in the art will appreciate that the therapeutically effective amount of cladribine administered may be lowered or increased by fine tuning and/or by administering cladribine with another active ingredient (see p. 24, lines 1-4). For example, cladribine may be administered with one or more additional active ingredients for the treatment of MS, such as the co-administration of cladribine with interferon-beta (see p. 24, lines 10-18), which addresses present claims 16 and 29 regarding the combined use of cladribine with interferon-beta.

With respect to the teachings of Bodor *et al.*, Applicants respectfully submit that the reference is silent with respect to the administration of cladribine therapy after the cladribine-free period of between about 8 and 10 months. Thus, Bodor *et al.* fail to teach a cladribine-free period of between about 8 and 10 months followed by a "maintenance period" during which a cladribine formulation is administered such that the total dose administered in the "maintenance period" is lower than the total dose first administered to the patient which is then followed by another cladribine-free period. Recognizing this issue, the Office Action argues that "it is implied that following these 10 months, treatment with cladribine is resumed" (Office Action at page 5). However, Applicants note that nowhere in the teachings of the reference is there any discussion about repeating a treatment course at any point in time at either the original dosage or at a lower dosage in a manner that could be construed as a "maintenance period". An obviousness rejection fails if the prior art relied on does not disclose all of the limitations of the claimed invention. *See, e.g., In re Zurko*, 258 F.3d 1379, 1385-86 (Fed. Cir. 2001). Thus, it is respectfully submitted that the teachings of Bodor *et al.* fail to disclose all of the limitations of the claimed invention and a *prima facie* case of obviousness cannot be based upon the teachings of Bodor *et al.*

It is also respectfully submitted that a factfinder should be aware of the distortion caused by hindsight bias. *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). In order to determine whether there was an apparent reason to combine known elements in the fashion claimed, the analysis should be made explicit. *KSR*, 127 S. Ct. at 1741 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". In this case, the Office Action has used the teachings of the as-filed specification of this application and improperly used hindsight reconstruction in order to utilize the teachings of Bodor *et al.* in the rejection of record (when making the argument that Bodor *et al.* imply "that treatment may begin again following a non-treatment period" (Office Action at pages 5 and 6)). *See Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

Continuing with the rejection, the Office Action argues that:

> Consistent with the teachings of Bodor, Grieb et al. teach the treatment of patients having relapsing-remitting MS comprising the oral administration of cladribine. Grieb discloses that cladribine was administered orally at 10 mg for 5 consecutive days, as 6 monthly courses followed by one or two additional courses at 3, 6 or 9 month intervals (see abstract and p. 324). In other words, Grieb teaches a treatment method comprising an initial treatment period of up to 6 months, followed by a non-treatment period of about 9 months, followed by another treatment cycle of about 6 months and non-treatment period of about 9 months, which treatment cycle could be repeated again. These teachings are on point to the presently recited (i) "induction period", (ii) "cladribine-free" period of about 8 to 10 months, (iii) "maintenance period", and (iv) "cladribine-free" period of claims 1, 9 and 17. The treatment was effective to provide a progressive reduction in lymphocytes to around 1000/μl on average (see abstract). Grieb also notes that the treatments were well tolerated, and with this dosing and schedule, cladribine seems relatively safe in MS patients (see abstract).
>
> Taken together, the combined teachings of Bodor et al. and Grieb et al. provide for a method of treating MS, including relapsing-remitting MS, comprising the oral administration of cladribine, wherein a treatment course comprises an initial treatment period of 2 to 6 months (which encompasses the instant 2 to 4 months) comprising the daily administration of cladribine for 5-7 days each month, followed by a non-treatment period (i.e., cladribine-free period) lasting 3 to 10 months (encompassing the instant 8 to 10 months), followed by another treatment period (i.e., a maintenance phase) of 2 to 6 months in which

> cladribine is administered for 5-7 days each month, followed again by another non-treatment period of 3 to 10 months. The treatment (i.e., maintenance)/non-treatment periods may be repeated once more according to Grieb and implied by Bodor. According to the combined teachings, it would therefore be possible to arrive at a final total dose of about 3.5 mg/kg at the end of the induction period if, for example, 10 mg cladribine is administered daily for 5 days each month for 4 months to a woman weighing about 58 kg (i.e., [4 x (10 mg x 5)] /58 kg = 3.45 mg/kg, which is about 3.5 mg/kg). As such, the ranges provided by the combined Bodor and Grieb references encompass the recited cladribine doses and dosing schedules of the present claims.
>
> The difference, therefore, is that neither of the above references teach that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase.

With respect to the teachings of Grieb *et al.*, Applicants respectfully submit that this reference, too, fails to provide the evidence necessary to arrive at the limitations of the claimed invention. For example, while Grieb *et al.* may teach that one can orally administer 10 mg of cladribine for 5 consecutive days, as 6 monthly courses followed by one or two additional courses at 3, 6 or 9 month intervals, the teachings of this reference also fail to disclose all of the limitations of the claimed invention (*i.e.*, an induction period of about two to four months).

The Office Action also relies upon the teachings of Bloom for additional teachings with respect to the treatment of multiple sclerosis and other autoimmune diseases. As indicated in the Office Action:

> Bloom discusses the treatment of MS and other autoimmune diseases, wherein effective treatment requires an intense induction phase during which time lymphocytes are continuously depleted from circulation to a level of less than 500 cells/μl, followed by a maintenance phase in a lower intensity treatment regimen to hold the overall blood lymphocyte count to less than 500 cells/μl (see columns 3-4). While the initial induction phase of treatment is accomplished in the Bloom reference by lymphoctapheresis and the maintenance phase of treatment is accomplished with the use of an immunosuppressive/immunomodulatory drug other than cladribine, the principle of Bloom's teachings remains the same: effective treatment of MS requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down. Even with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4 lines 39-49 regarding the use of azathioprine (AZA) and prednisone). Thus, based upon the teachings of Bloom, the ordinarily skilled artisan would have recognized that effective treatment of MS involves the removal of the majority of activated

lymphocytes from the patient in an initial treatment phase, followed by a maintenance phase in which the numbers of lymphocytes are maintained a reduced level. The person of ordinary skill would have also been aware that cladribine is useful in treating MS because it is an immunosuppressive agent that functions by reducing the numbers of activated lymphocytes (and in particular, monocytes, which are presumably activated against self-antigens). Particularly in view of the chronic nature of multiple sclerosis, in order to reduce the severity or duration of future relapses (or to prevent them altogether) the artisan would have been aware that long-term treatment success would require a therapy that is sustainable and well-tolerated by the patient.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat multiple sclerosis with oral cladribine according to a cyclic treatment regimen, wherein treatment involves an intense induction phase followed by a maintenance phase, and wherein the total dosage administered in the maintenance phase is less than the total dosage administered in the induction phase. Additionally, even though cladribine therapy is taught as being generally well-tolerated with a low incidence of adverse effects (see Bodor reference), in order to reduce the overall treatment costs associated with cladribine therapy and further lessen the risk of adverse side effects, the artisan would have been motivated to use a lower dose in subsequent treatment periods (i.e., the maintenance phase) that is still sufficient to sustain a therapeutically-effective immunosuppressive state. This idea is also presented in the teachings of Bloom, which suggest that subsequent rounds of treatment with an immunomodulatory agent should be at a lower overall dose(s) than the initial treatment with the agent. The artisan would have had a reasonable expectation that such a method comprising the oral administration of cladribine would be successful in the treatment of MS based upon the demonstrated effectiveness in reducing activated lymphocytes reported by Grieb and the general knowledge in the art with respect to the use of cladribine for treating MS (see, for example US Patent 5,506,214 to Beutler, listed on IDS).

As noted at column 4, lines 18-52 of Bloom, both lymphocytapheresis and a chemotherapeutic protocol are administered to an individual to hold lymphocyte numbers down to the desired levels (less than 500 cells/μL). It is unclear how this combined therapeutic regimen, including a combination of immunosuppressive drugs (azathioprine (AZA) and prednisone) added to lymphocytapheresis can be construed as "a more moderate maintenance phase" or a "lower intensity treatment regimen". If anything, this combination protocol taught in Bloom would have been considered a more intense treatment regimen since both lymphocytapheresis and immunosuppression via AZA and prednisone were being employed on the subject.

Turning to the argument that "[e]ven with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4, lines 39-49 regarding the use of azathioprine (AZA) and prednisone)". Applicants submit that this is an overstatement of the teachings of the reference. While it is true that the dosage of AZA and prednisone is lowered during the course of administration, the AZA dose is lowered from 5 mg/kg/day to 2.5 mg/kg/day over the span of five (5) days where it is held constant for the course of treatment (at 2.5 mg/kg). Likewise, prednisone is reduced from 60 mg/kg/day to 15 mg/kg/day over the span of 10 weeks and held constant at that dosage (15 mg/kg/day) for at least one year. Thus, it is clear that Bloom does not teach lowering treatment dosages with each successive use of the drug; rather Bloom teaches the administration of an initial loading dose of therapeutic agent followed by tapering the dosage of each drug to maintenance dosages that remain stable and are used throughout the treatment protocol.

The Office Action also argues that the therapeutically effective amount of cladribine can be lowered or increased by fine tuning or administering cladribine with another therapeutic agent (*e.g.*, interferon-beta) and that treatment durations, frequency of treatment and administered dosages are clearly recognized result–effective variables that a person skilled in the art would routinely optimize. Applicants respectfully disagree with this position and respectfully submit that the teachings of the cited references do not support a position that one skilled in the art would shorten the duration of what the Office Action construes as the "induction period" from the teachings of the cited references.

As noted in Grieb *et al.*, lymphocyte counts are not maximally suppressed until the individuals have been treated for at least six months (see page 326, column 2 and Figure 1). Thus, any optimization of that parameter would necessarily involve the administration of cladribine for at least six months in order to optimize the suppression of lymphocytes within a treated population. This teaching would be equally applicable to the teachings of Bodor *et al.*, especially since such information is not provided in the teachings of the Bodor *et al.* reference. Accordingly, Applicants respectfully submit that one skilled in the art, seeking to optimize the dosing regimens taught in either Bodor *et al.* or Grieb *et al.*, would have utilized a dosing

regimen of at least six months in order to optimize (maximize) the depletion of lymphocytes in view of the teachings of Grieb *et al.*

Applicants also note that a *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). Furthermore, an inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements in the manner asserted (*See DePuy Spine, Inc. v. Medtonic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed.Cir.2009). In this case, Applicants respectfully submit that the teachings of Grieb *et al.* undermine the reasons proffered as to why one skilled in the art would utilize an induction period of two to four months and teaches away from the use of a two to four month induction period as recited in the claims of this application. As noted above, Grieb *et al.* clearly teach that maximal reduction in lymphocyte numbers is observed after six months of treatment with cladribine. Thus, one skilled in the art would not have been led to shorten the "induction period" from six months to the two to four months as recited in the claims of this application. Rather, one skilled in the art would have been led to administer cladribine for a period of six months (as the "induction period") in order to maximally suppress lymphocyte counts (an outcome clearly indicated as desirable by Grieb *et al.*, Bodor *et al.* and Bloom and argued as such in the Office Action at page 9, first full paragraph). Accordingly, Applicants respectfully assert that the claimed invention is not obvious over the cited references and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb

Electronic Acknowledgement Receipt

EFS ID:	12323505
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	16-MAR-2012
Filing Date:	23-APR-2010
Time Stamp:	14:11:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amd.pdf	1225077 925df8596ec048901c260143bdbb67bc404bffd3	yes	11

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	Applicant Arguments/Remarks Made in an Amendment	4	11
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

23557 7590 05/24/2012

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
05/24/2012	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	12/766,173	DE LUCA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *16 March 2012*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *1-29* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-29* is/are rejected.

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☒ All b)☐ Some * c)☐ None of:

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

2.☒ Certified copies of the priority documents have been received in Application No. 11/722,018.

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

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

Attachment(s)

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

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims **1-29** are pending and under examination in the current office action.

2. With respect to the objection to specification, the examiner notes that box 10 on form PTOL-326 was inadvertently checked, and regrets any confusion this may have caused.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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

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

3. Claims **1-29** stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 7,713,947. As discussed in the previous office action, although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass the therapeutic oral administration of cladribine for the treatment of multiple sclerosis. The rejection is maintained for reasons of record and therefore will not be reiterated here.

4. Claims **1-29** stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-71 and 79 of copending Application No. 12/301,083. As discussed in the previous office action, although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass the therapeutic administration of cladribine in combination with interferon-beta for the treatment of patients suffering from multiple sclerosis (MS), including progressive MS and relapsing-remitting MS. The rejection is maintained for reasons of record and therefore will not be reiterated here.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

5. In the response filed March 16, 2012, Applicants note that a Terminal Disclaimer can be filed and request that the above rejections be held in abeyance until such time as allowable subject matter is identified.

6. Applicants' request has been fully considered. The above rejections are held in abeyance until such time as allowable subject matter is identified.

Claim Rejections - 35 USC § 103

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

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

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims **1-29** stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2004/087101 A2 by Bodor et al. and Grieb et al. (*Arch. Immunol. Therap. Exp.* 1995; 43:323-327) in view of US Patent 4,964,848 to Bloom. The rejection is maintained for reasons of record and as discussed below.

The reasons why the combined reference teachings render obvious the presently claimed invention have been discussed previously and thus for the sake of brevity will not be reiterated here.

Response to Arguments

8. In the response filed March 16, 2012, Applicants argue that the Bodor et al. reference is silent with respect to the administration of cladribine therapy after the cladribine-free period of between about 8 and 10 months. Applicants assert that Bodor fails to teach a cladribine-free period of about 8 to 10 months followed by a "maintenance period" during which a cladribine formulation is administered at a lower dose then the total dose first administered to the patient, which is then followed by another cladribine-free period. Applicants insist that nowhere in Bodor does it discuss repeating a treatment course at any time point. According to Applicants, the examiner has used improper hindsight reconstruction in order to utilize the teachings of Bodor in making the argument that Bodor implies that "treatment may begin again following a non-treatment period".

With respect to the Grieb et al. reference, Applicants submit that this reference fails to disclose all of the limitations of the claimed invention (i.e., an induction period of

about two to four months). And regarding the Bloom reference, Applicants remark that in contrast to the remarks of the previous office action, the combined therapeutic regimen of a combination of immunosuppressive drugs (azathioprine (AZA) and prednisone) added to lymphocytapheresis would have been considered a more intense treatment regimen rather than a lower intensity treatment regimen. Applicants further argue that Bloom does not teach lowering treatment dosages with each successive use of the drug, but rather teaches the administration of an initial loading dose of agent followed by tapering the dosage of each drug to maintenance dosages that remain stable and are used throughout the treatment protocol.

Additionally, Applicants contend the teachings of the cited references do not support a position that one of skill in the art would shorten the duration of the "induction period". According to Applicants, the Grieb et al. reference indicates that lymphocytes counts are not maximally suppressed until the individual have been treated for at least six months. Therefore, Applicants submit that one skilled in the art seeking to optimize the dosing regimens in either Bodor or Grieb would have utilized a dosing regimen of at least six months in order to optimize (maximize) the depletion. In this respect, Applicants argue that the teachings of Grieb constitute a teaching away from the use of an induction period of two to four months, and instead would have led the skilled artisan to administer cladribine for a period of six months in order to maximally suppress lymphocyte counts.

9. Applicants' arguments have been fully considered but are not persuasive. In response to applicants' arguments against the references individually, one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Bodor clearly teaches a method comprising orally administering cladribine for two months "followed by ten months of no treatment". This teaching is directly on point to steps (i) and (ii) of the methods of claims 1, 9 and 17. Contrary to Applicants' arguments, there is nothing else that Bodor could have meant by this statement other than no treatment (i.e., no drug) was given for ten months. As such, this statement necessarily suggests that *a treatment* was administered at the conclusion of the ten-month drug-free period, otherwise the "no treatment" period would just keep continuing and there would have been no need to indicate a specific length of time for this "non-treatment" period. Because Bodor does not disclose any therapy for the treatment of multiple sclerosis (MS) other than one which comprises cladribine, this again would suggest to one of ordinary skill in the art that cladribine therapy was *resumed* at the end of the ten-month non-treatment period. This interpretation is consistent with the language used by Bodor in the Examples, in which cladribine treatment days were separated by a "drug-free interval of at least 5 days" (see paragraph spanning pp. 33-34). In other words, periods of non-treatment separated periods of cladribine treatment. Therefore, Bodor does implicitly teach that cladribine administration may be repeated following the "ten months of no treatment".

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, even if, assuming *arguendo*, the ordinarily skilled artisan would not have taken Bodor's therapeutic regimen comprising "ten months of no treatment" to imply that treatment should be resumed at the end of this period, the artisan would still have had general knowledge about the treatment of multiple sclerosis (MS) therapy to rely upon and which was within the level of ordinary skill at the time of filing. This knowledge would have included the teachings of Grieb, which clearly indicate a repetitive treatment regimen comprising periods of cladribine therapy separated by periods of no treatment (i.e., cladribine-free periods). In this respect also, it is irrelevant that the Bodor or Grieb references allegedly do not individually teach each of the presently claimed limitations, because as discussed above the conclusion of obviousness is based upon that which the references would have suggested *collectively*, not individually. Accordingly, it would have been obvious to the person of ordinary skill to provide a therapy for MS that comprised a cyclical dosing paradigm, with periods of cladribine treatment lasting about two months interspersed by drug-free periods of about 10 months.

With respect to the Bloom, it is noted that the reference has been relied upon for its general teachings of the treatment of autoimmune disease, including MS, and to demonstrate what knowledge would be available to one of ordinary skill in the art at the

time of filing. As discussed previously, Bloom teaches a two phase treatment protocol comprising an induction phase and a maintenance phase. While the induction phase of treatment is accomplished in the Bloom reference by lymphoctapheresis and the maintenance phase of treatment is accomplished with the use of an immunosuppressive/immunomodulatory drug other than cladribine in addition to occasional lymphocytaphersis (i.e., once every 3-4 weeks in the maintenance phase versus 3-5 times per week in the induction phase), the principle of Bloom's teachings remains the same: effective treatment of MS requires an intense induction phase with substantial depletion of blood lymphocytes followed by a maintenance phase to hold the cell numbers down. Note that Bloom teaches that the induction phase lasts about 5 to 7 weeks (see column 4, lines 3-4), which on the longer side (7 weeks) is again consistent with the induction period of “about 2 months” in the presently claimed invention.

In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., lowering treatment dosages with each successive use of the drug) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Not that the claims only recite that the *total dose* of cladribine reached at the end of the mainteance period is less than the *total dose* of cladribine reached at the end of the induction period. There is nothing recited in the claims that states that each successive use of cladribine as at a lower dose. Once the maintenance period is reached and steps (iii) and (iv) are repeated,

subsequent cladribine treatments are administered at the lower dosage level compared to the induction dosage, but are not necessarily lower with respect to each round of treatment. In this respect, the teachings of Bloom are directly on point to the presently claimed invention as indicated by applicant, in which Bloom teaches “the administration of an initial loading dose of agent followed by tapering the dosage of each drug to maintenance dosages that remain stable and are used throughout the treatment protocol.” One of skill in the art, such as a pharmacist, M.D., Ph.D. other medical professional, would have understood the routine practice of using a loading dose of an agent (which is typically a high dose to initiate treatment) followed by lowered maintenance doses of the agent. Bloom is exemplary of this standard knowledge.

Finally, with respect to the argument that the Grieb et al. reference teaches away from the present invention, applicants' argument is not persuasive. A true “teaching away" from a concept must be explicit, not just an otherwise general suggestion. There is nothing in Grieb that explicitly teaches away from using an induction period of less than six months. In fact, Grieb notes that the decrease in the average lymphocyte counts during treatment with cladribine is statistically significant from the second month of therapy (see Fig. 1 at p. 324). Thus, in view of the explicit teachings of Bodor indicating a cladribine treatment period of two months, and the teachings of Grieb indicating that cladribine treatment significantly reduced lymphocyte numbers by the second month of treatment, which lymphocyte decrease plateaued at around five months of treatment (again see Fig. 1 of Grieb), it would have been obvious to provide cladribine treatment periods of about two to about five months, which is on point to the

presently recited "about 2 months to about 4 months" of the claimed invention. Accordingly, the combined teachings of the above references still render obvious the presently recited invention of claims 1-29, and the rejection is maintained.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

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

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

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	106	De-luca-g$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:57
L2	15	ythier-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:57
L3	6	munafo-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:57
L4	6	lopez-bresnahan-m$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:57
L5	394	merck-serono-$.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:57
L6	9446	2cda cladribine 2-chlorodeoxyadenosine litak moectro	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:58
L7	29	l6 and l5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 20:58
L8	86589	multiple adj sclerosis	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:00
L9	2996	l6 and l8	US-PGPUB; USPAT;	OR	OFF	2012/05/13 21:00

			USOCR; FPRS; EPO; JPO; DERWENT			
L10	2899	l9 and oral$	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:00
L12	25609	"ifn.beta." interferon-beta (interferon near beta) (ifn near beta)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/05/13 21:01
L13	1568	l10 and l12	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:01
L14	15	ythier-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:03
L15	6	lopez-bresnahan-m$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:03
L16	9408	2cda cladribine 2-chlorodeoxyadenosine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:03
L17	61	L16 same2 (("1.5" "1.6." "1.7" "1.8" "1.9" "2.0" L14 "2.1" "2.2" "2.3" "2.4" "2.5" "2.6" "2.7" "2.8" "2.9" "3.0" "3.1" "3.2" "3.3" "3.4" "3.5" "3.6" "3.7" "3.8" "3.9" L15 "4.0") with mg/kg)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:03
L18	61	L6 same2 (("1.5" "1.6." "1.7" "1.8" "1.9" "2.0" L14 "2.1" "2.2" "2.3" "2.4" "2.5" "2.6" "2.7" "2.8" "2.9" "3.0" "3.1" "3.2" "3.3" "3.4" "3.5" "3.6" "3.7" "3.8" "3.9" L15 "4.0") with mg/kg)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:03
L19	25482	(loading adj dose) (induction near (phase period dos$3 regimen))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/05/13 21:12
L20	115	l13 and l19	US-PGPUB; USPAT;	OR	OFF	2012/05/13 21:12

			USOCR; FPRS; EPO; JPO; DERWENT			

EAST Search History (Interference)

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5/ 13/ 2012 9:19:46 PM
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12766173	DE LUCA ET AL.
	Examiner	Art Unit
	KIMBERLY A BALLARD	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (PALM, EAST, NPL)	12/09/2011	KAB
EAST (USPAT, USOCR, USPGPUB, DERWENT, EPO, JPO, FPRS)	12/09/2011	KAB
STN (MEDLINE, BIOSIS, CAPLUS, EMBASE)	12/09/2011	KAB
PLUS search	12/09/2011	STIC
Updated text searches in EAST	05/13/2012	KAB

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
	Inventor & Assignee search - see EAST search	12/09/2011	KAB

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May 24, 2012 05:28:01 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	CTFR	05/24/2012	SER.125D1

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Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 24, 2012.

Frank C. Eisenschenk, Ph.D., Patent Attorney

RESPONSE UNDER 37 C.F.R. § 1.116
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Serial No.	:	12/766,173
Filed	:	April 23, 2010
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

RESPONSE UNDER 37 C.F.R. § 1.116

Sir:

The remarks that follow are submitted for the Examiner's consideration in the above-referenced patent application in response to the Office Action dated May 24, 2012.

Remarks

Claims 1-29 are pending in the subject application and currently before the Examiner. Favorable consideration of the pending claims in view of the arguments presented herein is respectfully requested.

Claims 1-29 are rejected under the doctrine of obviousness-type double patenting over claims 1-48 of U.S. Patent No. 7,713,947 and claims 1-29 are provisionally rejected for obviousness-type double patenting over claims 42-71 and 79 of co-pending application 12/301,083. Applicants acknowledge that a Terminal Disclaimer can be filed to overcome this rejection and respectfully request that this issue be held in abeyance until such time as allowable subject matter is identified.

Claims 1-29 are rejected under 35 U.S.C. § 103(a) as obvious over Bodor *et al.* (WO 2004/087101 and Grieb *et al.* (1995) in view of Bloom (U.S. Patent 4,964,848). The Office Action indicates that the Bodor *et al.* and Grieb *et al.* references teach the use of cladribine administered orally for the treatment of patients having multiple sclerosis (MS) and are cumulative in nature. The Office Action states:

> Specifically, Bodor *et al.* disclose the administration of a therapeutically effective amount of cladribine via oral administration for the treatment of MS, wherein 10 mg of cladribine is administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Here, because Bodor states "10 months of no treatment", it is implied that following these 10 months, treatment with cladribine is resumed. Hence, Bodor teaches an "induction period" of treatment that is about 2 months followed by a cladribine-free period of about 10 months, wherein it is implied that treatment may begin again following the nontreatment period, which is on point to limitations within claims 1, 3, 6, 9, 17, 19 and 22 reciting a treatment method comprising an induction period and a cladribine-free period. Also, Bodor discloses that the daily dose of cladribine administered is 10 mg, which addresses present claims 11, 12, 25 and 26 (*i.e.*, the formulation is administered at a daily dose of 3 to 30 mg cladribine; a daily dose of 10 mg cladribine). This dose is taught to be administered for 5-7 days per month, which meets the limitation of claims 13 and 27 (*i.e.*, the formulation is orally administered 1 to 7 days per month during the induction period). Thus, for 7 days of treatment each month for 2 months, and for an average adult human weighing approximately 65 kg, the total dose of cladribine reached at the end of this period would be 2.15 mg/kg (*i.e.*, (2 x (10 mg x 7)) / 65 kg), which is within the range of about 1.7 mg/kg to about 3.5 mg/kg as in base claims 1 and 17. However, it is clear that the total dose reached at the end of the initial treatment

period is dependent upon the number of days cladribine is being administered per month (*i.e.*, 5 to 7) and the weight of the patient being administered the treatment. For example, a woman weighing approximately 58 kg and treated for 2 months with 10 mg cladribine daily for 5 days per month would reach a total dose of 1.72 mg/kg, which would be on point to claims 4 and 20 (*i.e.*, the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg).

Further, Bodor teaches that one of skill in the art will appreciate that the therapeutically effective amount of cladribine administered may be lowered or increased by fine tuning and/or by administering cladribine with another active ingredient (see p. 24, lines 1-4). For example, cladribine may be administered with one or more additional active ingredients for the treatment of MS, such as the co-administration of cladribine with interferon-beta (see p. 24, lines 10-18), which addresses present claims 16 and 29 regarding the combined use of cladribine with interferon-beta.

Continuing with the rejection, the Office Action argues that:

Consistent with the teachings of Bodor, Grieb *et al.* teach the treatment of patients having relapsing-remitting MS comprising the oral administration of cladribine. Grieb discloses that cladribine was administered orally at 10 mg for 5 consecutive days, as 6 monthly courses followed by one or two additional courses at 3, 6 or 9 month intervals (see abstract and p. 324). In other words, Grieb teaches a treatment method comprising an initial treatment period of up to 6 months, followed by a non-treatment period of about 9 months, followed by another treatment cycle of about 6 months and non-treatment period of about 9 months, which treatment cycle could be repeated again. These teachings are on point to the presently recited (i) "induction period", (ii) "cladribine-free" period of about 8 to 10 months, (iii) "maintenance period", and (iv) "cladribine-free" period of claims 1, 9 and 17. The treatment was effective to provide a progressive reduction in lymphocytes to around 1000/μl on average (see abstract). Grieb also notes that the treatments were well tolerated, and with this dosing and schedule, cladribine seems relatively safe in MS patients (see abstract).

Taken together, the combined teachings of Bodor *et al.* and Grieb *et al.* provide for a method of treating MS, including relapsing-remitting MS, comprising the oral administration of cladribine, wherein a treatment course comprises an initial treatment period of 2 to 6 months (which encompasses the instant 2 to 4 months) comprising the daily administration of cladribine for 5-7 days each month, followed by a non-treatment period (*i.e.*, cladribine-free period) lasting 3 to 10 months (encompassing the instant 8 to 10 months), followed by another treatment period (*i.e.*, a maintenance phase) of 2 to 6 months in which cladribine is administered for 5-7 days each month, followed again by another non-treatment period of 3 to 10 months. The treatment (*i.e.*, maintenance)/non-treatment periods may be repeated once more according to Grieb and implied by Bodor. According to the combined teachings, it would therefore be possible to arrive at a final total dose of about 3.5 mg/kg at the end of the induction period if,

> for example, 10 mg cladribine is administered daily for 5 days each month for 4 months to a woman weighing about 58 kg (*i.e.*, [4 x (10 mg x 5)] /58 kg = 3.45 mg/kg, which is about 3.5 mg/kg). As such, the ranges provided by the combined Bodor and Grieb references encompass the recited cladribine doses and dosing schedules of the present claims.
>
> The difference, therefore, is that neither of the above references teach that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase.

With respect to the teachings of Bodor *et al.*, Applicants respectfully submit that the reference is silent with respect to the administration of cladribine therapy after the cladribine-free period of between about 8 and 10 months. Furthermore, Grieb *et al.* teach an induction period of six months (where five consecutive doses of cladribine were administered as six monthly courses followed by one or two additional courses at three or six month intervals). This is in contrast to the alleged teachings of Grieb *et al.* cited in the Office Action where it is argued that the reference teaches "**an initial treatment period of up to 6 months**, followed by a non-treatment period of about 9 months, followed by another treatment cycle of about 6 months and non-treatment period of about 9 months, which treatment cycle could be repeated again" (Office Action dated December 19, 2011 at page 7; emphasis added). Furthermore, using the weight of a "patient" as set forth in the Office Action of December 19, 2011 at page 6 (a female at 58 kg or a male at 65 kg), a total dose of 5.17 or 4.61 mg/kg of cladribine would be administered to a patient according to the teachings of Grieb *et al.* Thus, one skilled in the art would have had to both reduce the length of the "induction period" taught in Grieb *et al.* and the "total dose" of cladribine administered to a patient in order to meet the limitations of the claimed invention. The teachings of Bodor *et al.* and/or Bloom *et al.* do not remedy this defect in the rejection set forth over Grieb *et al.* and, thus, a *prima facie* case of obviousness has not been established for the claimed invention.

Bodor *et al.* teach two dosing regimens: 1) an induction period of two months (during which 10 mg of cladribine are administered for 5-7 days in each month) followed by a 10 month period of time in which the patient receives no treatment and 2) an induction period of six months during which 10 mg of cladribine is administered each day for a period of 5 to 7 days followed by an 18 month period of time during which no cladribine is administered. Applicants

respectfully submit that the second dosing regimen of Bodor *et al.* (corresponding to the six month induction period) clearly fails to meet the limitations of the claimed invention and there is no motivation (in view of Grieb *et al.* and/or Bloom *et al.*) to alter this dosing regimen such that it meets the limitations of the claimed invention). Turning to the first dosing regimen and the argument that "it is implied that following these 10 months, treatment with cladribine is resumed", Applicants note that nowhere in the teachings of the reference is there any discussion about repeating a treatment course at any point in time at either the original dosage or at a lower dosage in a manner that could be construed as a "maintenance period" as defined by the subject application.

Even if one were to accept this "implied" teaching in Bodor *et al.*, the teachings of the reference would not lead one of ordinary skill in the art to the claimed invention. Specifically, one skilled in the art would not have had any reason to reduce the dosage of cladribine administered during the "maintenance period" as recited in the claims such that the total dosage of cladribine administered to the patient is less than the total dose of cladribine the patient received during the induction period. Rather, the teachings of the reference would suggest that the same dosing regimen be applied to the patient (10 mg of cladribine administered for 5-7 days each month for two consecutive months followed by another 10 month period of time in which the patient receives no treatment). This would have resulted in the same total dose of cladribine being administered to the patient in both the induction phase and the maintenance phase. Thus, the combined teachings of the references would not have led one skilled in the art to a dosing regimen and/or total dosages recited in claims 1, 4, 5, 9, 10, 17, 20 or 21.

Recognizing that such is the case, the Office Action argues that the cladribine dose can be lowered or raised by fine tuning or administration with other therapeutic agents suitable for treating multiple sclerosis (see Office Action dated December 19, 2011, paragraph bridging pages 6-7). The Final Rejection indicates, at page 9, that Bloom *et al.* is relied upon for a general teaching of the treatment of autoimmune diseases, such as multiple sclerosis, and to demonstrate what knowledge was available to those skilled in the art at the time the invention was made. Particularly, the Office Action argues that those skilled in the art recognize that one would initiate a treatment with a "loading dose" of a therapeutic agent followed by lower maintenance doses of the therapeutic agent. However, such a modification of the teachings of

Bodor *et al.* or Grieb *et al.* is not supported by the teachings of the individual references and one skilled in the art, in view of Bodor *et al.* and/or Grieb *et al.* would not have been motivated to reduce the dosage of cladribine administered to a patient in view of the teachings of the references.

Furthermore, even if the arguments set forth in the Office Action are accurate (*i.e.*, that those skilled in the art recognize that one would initiate a treatment with a "loading dose" of a therapeutic agent followed by lower maintenance doses of the therapeutic agent), it is telling that the inventors/authors of Bodor *et al.* and Grieb *et al.* (presumed to be those of ordinary skill in the art) do not indicate that one should use a higher "loading dose" followed by a lower "maintenance dose" of cladribine. Indeed, if this were the case, the one skilled in the art, in view of Bodor *et al.* or Grieb *et al.* would have administered the first dose of cladribine in a given course at a higher "loading dose" and the second through final doses of that course would have been administered at the lower "maintenance dose". Following such a course of action would not have allowed one of ordinary skill in the art to arrive at the claimed invention (*i.e.*, as recited in claims 1, 4, 5, 9, 10, 17, 20 or 21).

Finally, Applicants disagree with arguments set forth in the Office Action with respect to the fact that one skilled in the art, in view of the combined teachings of the references, would have been motivated to alter the "induction period" taught in Grieb *et al.* or Bodor *et al.* from two months or six months (as explicitly taught in the references) to the claimed two to four month "induction period" because Grieb *et al. et al.* teaches that cladribine administration significantly reduced lymphocyte numbers in the second month of therapy and reached a nadir around the fifth month of therapy. Applicants respectfully disagree with this position, particularly in view of the teachings of Bloom *et al.* Specifically, Bloom *et al.* teach that, for the treatment of multiple sclerosis, it is desirable to lower lymphocyte counts to less than 500 cells/μL and preferably to less than 300 cells/μL and thereafter continuing such treatments while administering an immunosuppressive compounds in amounts sufficient to maintain lymphocyte counts at less than 500 cells/μL and preferably less than 300 cells/μL. Indeed, the Office Action dated December 19, 2011 explicitly relied on such teachings at pages 8-9 in establishing the obviousness rejections of record. Thus, one skilled in the art would not have been motivated to alter a therapeutic regimen in a manner that would permit more lymphocytes to survive a

treatment protocol. Rather, one skilled in the art would have been motivated to follow the teachings of Grieb *et al.* and administer cladribine until such time as lymphocyte numbers reached a nadir and treat the patient to maintain such numbers of lympohocytes (*i.e.*, treat the patient with cladribine for six months as discussed in the reference and illustrated in Figure 1 of Grieb *et al.*) Thus, one of ordinary skill in the art, if anything, would have been motivated to increase the duration of cladribine administration to ensure that lymphocyte numbers were maximally reduced. Accordingly, it is respectfully submitted that the claimed invention is not obvious over the teachings of Bodor *et al.* and Grieb *et al.* in view of Bloom and reconsideration and withdrawal of the rejection is respectfully requested.

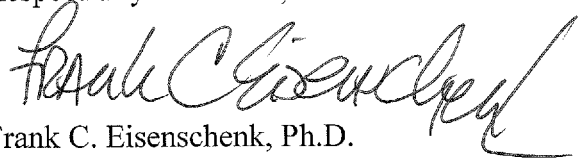
Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb

Electronic Acknowledgement Receipt

EFS ID:	13580377
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	24-AUG-2012
Filing Date:	23-APR-2010
Time Stamp:	12:12:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Resp-final.pdf	605081 2c9b19096b9abf09e7eca83c583255be173c5cdd	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	7

Warnings:	
Information:	
Total Files Size (in bytes):	605081

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

23557 7590 09/07/2012

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
09/07/2012	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/766,173	**Applicant(s)** DE LUCA ET AL.
	Examiner Kimberly A. Ballard	**Art Unit** 1649

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

THE REPLY FILED 24 August 2012 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;

(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

STATUS OF CLAIMS

14. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: 1-29.
Claim(s) withdrawn from consideration: .

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

Continuation of 5. Applicant's reply has overcome the following rejection(s): the rejection of claims 1-29 under 35 USC 103(a) (Bodor in view of Grieb and Bloom).

Continuation of 11. does NOT place the application in condition for allowance because: Although the obviousness rejection under 35 USC 103 is withdrawn in view of Applicant's persuasive arguments, the obviousness-ypte double patenting rejections are maintained for reasons of record. Because all other issues of patentability have been overcome, Applicant must supply a terminal disclaimer(s) or appropriate arguments to address/overcome the double-patenting rejections of record.

Okay to Enter. /KAB/ 08/30/2012

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 24, 2012.

Frank C. Eisenschenk, Ph.D., Patent Attorney

RESPONSE UNDER 37 C.F.R. § 1.116
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Serial No.	:	12/766,173
Filed	:	April 23, 2010
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

RESPONSE UNDER 37 C.F.R. § 1.116

Sir:

The remarks that follow are submitted for the Examiner's consideration in the above-referenced patent application in response to the Office Action dated May 24, 2012.

To: euspto@slepatents.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23557

Sep 07, 2012 05:27:19 AM

Dear PAIR Customer:

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23557 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
12766173	CTAV	09/07/2012	SER.125D1

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on September 10, 2012.

Frank C. Eisenschenk, Ph.D., Patent Attorney

RESPONSE UNDER 37 C.F.R. § 1.116
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Serial No.	:	12/766,173
Filed	:	April 23, 2010
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

SUPPLEMENTAL RESPONSE UNDER 37 C.F.R. § 1.116

Sir:

Applicants request that the period for response be extended one month through and including September 24, 2012, the fee for which was paid at the time this Amendment was filed.

The remarks that follow are submitted for the Examiner's consideration in the above-referenced patent application in response to the Advisory Action dated September 7, 2012 and the Office Action dated May 24, 2012.

Remarks

Claims 1-29 are pending in the subject application and currently before the Examiner. Favorable consideration of the pending claims in view of the arguments presented herein is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 1-29 remain rejected under the doctrine of obviousness-type double patenting over claims 1-48 of U.S. Patent No. 7,713,947 and claims 1-29 are provisionally rejected for obviousness-type double patenting over claims 42-71 and 79 of co-pending application 12/301,083. However, in order to expedite prosecution of the subject application, Applicants are submitting a Terminal Disclaimer simultaneously with this Response which obviates this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/asl

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Electronic Patent Application Fee Transmittal

Application Number:	12766173
Filing Date:	23-Apr-2010
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Attorney Docket Number:	SER.125D1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	150	150

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**150**

Electronic Acknowledgement Receipt

EFS ID:	13697057
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	10-SEP-2012
Filing Date:	23-APR-2010
Time Stamp:	13:33:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$150
RAM confirmation Number	12699
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Supplemental Response or Supplemental Amendment	Resp-final-supp.pdf	124403 bc967f692541c9c0be509604d40aeb1f7768cb9f	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29915 9835d9c4ac1a4d38abcc5f0d4de7fc95ad39f53c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	154318		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	12766173
Filing Date	23-Apr-2010
First Named Inventor	Giampiero De Luca
Attorney Docket Number	SER.125D1
Title of Invention	Cladribine Regimen for Treating Multiple Sclerosis

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
MERCK SERONO SA	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

12301083 filed on 11/17/2008

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

( ) Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

( ) Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

( ) Applicant(s) status remains as SMALL ENTITY.

(●) Applicant(s) status remains as other than SMALL ENTITY.

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

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 45332

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors

( ) A joint inventor; all of whom are signing this request

( ) The assignee of record of the entire interest that has properly made itself of record pursuant to 37 CFR 3.71

Signature	/FRANK C. EISENSCHENK/

Name	FRANK C. EISENSCHENK, PH.D.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	12766173
Filing Date:	23-Apr-2010
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Attorney Docket Number:	SER.125D1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or terminal disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 12766173

Filing Date: 23-Apr-2010

Applicant/Patent under Reexamination: De Luca et al.

Electronic Terminal Disclaimer filed on September 10, 2012

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	13697174
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	Cladribine Regimen for Treating Multiple Sclerosis
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	10-SEP-2012
Filing Date:	23-APR-2010
Time Stamp:	13:43:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	44
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	36493 a56e53a1e4bfee692b4d47c01b5eb0993b08c970	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29916 f1403b19204b7c6f090d88cb0975b005c633257f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	66409		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23557 7590 10/23/2012

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER
BALLARD, KIMBERLY

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/23/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/23/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23557 7590 10/23/2012

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/23/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
BALLARD, KIMBERLY	1649	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

23557 7590 10/23/2012

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/23/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 162 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 162 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/766,173	DE LUCA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the after-final response and terminal disclaimers filed 09/10/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-29*.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☒ Certified copies of the priority documents have been received in Application No. *11/722,018* .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	108	De-luca-g$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:20
L3	15	ythier-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:20
L5	6	munafo-a$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:21
L7	6	lopez-bresnahan-m$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:22
L8	11	bresnahan-m$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:22
L11	430	merck-serono-$.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:22
L12	10357	cladribine 2cda 2-chlorodeoxyadenosine litak movectro	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:23
L13	35	l11 and l12	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:23
L15	10996514	(multiple adj sclerosis) ms	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:24
L16	9235	l12 and l15	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:25
L17	90360	multiple adj sclerosis	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:25
L18	3312	l17 and l12	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:25

L19	16495	"ifn-.beta" interferon-beta ifn-beta "beta.-ifn" beta-interferon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:26
L20	896	l19 and l18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:26
L21	3207	l18 and oral$	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:26
L22	871	l21 and l19	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:28
L23	785	l20 and (weeks months)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:28
L24	606756	(combination combined adjunct) with (therapy treatment agent therapeutic)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:32
L25	772	l23 and L24	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:32
L26	59724	((initial first loading) near2 dose) (induction near (phase period dos$3 regimen))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:38
L27	940334	(maintain$3 maintenance) with (dos$3 level period)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:40
L28	205	l27 and l26 and l25	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:41
L29	725	(cladribine 2cda 2-chlorodeoxyadenosine litak movectro).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:48
L30	190	l29 and l17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/10/17 14:48

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	25	De-luca-g$.in.	USPAT; UPAD	OR	ON	2012/10/17 14:20
L4	3	ythier-a$.in.	USPAT; UPAD	OR	ON	2012/10/17 14:21
L6	1	munafo-a$.in.	USPAT;	OR	ON	2012/10/17

			UPAD			14:21
L9	1	lopez-bresnahan-m$.in.	USPAT; UPAD	OR	ON	2012/10/17 14:22
L10	4	bresnahan-m$.in.	USPAT; UPAD	OR	ON	2012/10/17 14:22
L14	85	merck-serono-$.as.	USPAT; UPAD	OR	ON	2012/10/17 14:24
L31	124	(cladribine 2cda 2-chlorodeoxyadenosine litak movectro).clm.	USPAT; UPAD	OR	ON	2012/10/17 14:48
L32	32	l31 and (multiple adj sclerosis)	USPAT; UPAD	OR	ON	2012/10/17 14:48

10/17/2012 2:51:54 PM
C:\Users\kballard\Documents\EAST\Workspaces\12.766173.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12766173	DE LUCA ET AL.
	Examiner	Art Unit
	KIMBERLY A BALLARD	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (PALM, EAST, NPL)	12/09/2011	KAB
EAST (USPAT, USOCR, USPGPUB, DERWENT, EPO, JPO, FPRS)	12/09/2011	KAB
STN (MEDLINE, BIOSIS, CAPLUS, EMBASE)	12/09/2011	KAB
PLUS search	12/09/2011	STIC
Updated text searches in EAST	05/13/2012	KAB
Updated text searches in EAST	10/17/2012	KAB

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
	Inventor & Assignee search - see EAST search	12/09/2011	KAB
	Inventor, assignee search updated - see EAST search	10/17/2012	KAB

Okay to Enter. /KAB/ 10/17/2012

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on September 10, 2012.

Frank C. Eisenschenk, Ph.D., Patent Attorney

RESPONSE UNDER 37 C.F.R. § 1.116
Patent Application
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Serial No.	:	12/766,173
Filed	:	April 23, 2010
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

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

SUPPLEMENTAL RESPONSE UNDER 37 C.F.R. § 1.116

Sir:

Applicants request that the period for response be extended one month through and including September 24, 2012, the fee for which was paid at the time this Amendment was filed.

The remarks that follow are submitted for the Examiner's consideration in the above-referenced patent application in response to the Advisory Action dated September 7, 2012 and the Office Action dated May 24, 2012.

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12766173	DE LUCA ET AL.
Examiner	**Art Unit**
KIMBERLY A BALLARD	1649

ORIGINAL		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
514	46	A	6	1	K	31 / 52 (2006.01.01)	A	6	1	K	9 / 00 (2006.01.01)
CROSS REFERENCE(S)		A	6	1	K	31 / 7076 (2006.01.01)					
		A	6	1	K	38 / 21 (2006.01.01)					

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	85.6				

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/KIMBERLY A BALLARD/ Examiner.Art Unit 1649	10/17/2012	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/ELIZABETH C KEMMERER/ Primary Examiner.Art Unit 1646	10/18/2012	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

To: euspto@slepatents.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23557

Oct 23, 2012 05:19:49 AM

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PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	NOA	10/23/2012	SER.125D1

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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23557 7590 10/23/2012
SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
Ph: (352)375-8100 Fax: (352)372-5800

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N/A - Filed EFS	(Depositor's name)
	(Signature)
	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	04/23/2010	Giampiero De Luca	SER.125D1	1906

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/23/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
BALLARD, KIMBERLY	1649	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 SALIWANCHIK, LLOYD & EISENSCHENK
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: MERCK SERONO SA

(B) RESIDENCE: (CITY and STATE OR COUNTRY): COINSINS, VAUD, SWITZERLAND

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
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☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

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☒ Payment by credit card. Form PTO-2038 is attached.
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5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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Authorized Signature _____ Date JANUARY 16, 2013

Typed or printed name FRANK C. EISENSCHENK, PH.D. Registration No. 45,332

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	12766173
Filing Date:	23-Apr-2010
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Attorney Docket Number:	SER.125D1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1770	1770
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2070**

Electronic Acknowledgement Receipt

EFS ID:	14710186
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	16-JAN-2013
Filing Date:	23-APR-2010
Time Stamp:	09:47:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2070
RAM confirmation Number	8347
Deposit Account	190065
Authorized User	EISENSCHENK, FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFeePaid.pdf	155219 cf1f04636ce5ca1339520b89dbbd79c8c4797217	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31828 00f2a8b3b56a371028cf0974d2f495d9015b4c2e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	187047		

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New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

In the Specification

Please substitute the following paragraph on page 9, beginning at line 5:

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, ~~polyvinyl~~ polyvinyl alcohol in water, etc. with a typical sugar coating.

Change(s) applied to document, /G.H./ 11/15/2012

Please substitute the following paragraph on page 9, beginning at ~~line 15~~ line 18:

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, ~~maizestarch~~ maize starch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl ~~sulfate)~~sulfate. Tablets may be coated according to methods well known in the art.

Please substitute the following paragraph on page 15, beginning at line 26:

In another embodiment, the invention provides a ~~a use~~use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/766,173	02/19/2013	8377903	SER.125D1	1906

23557 7590 01/30/2013

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 162 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Giampiero De Luca, Conches/Geneva, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

To: euspto@slepatents.com,,
From: PAIR_eOfficeAction@uspto.gov
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Jan 31, 2013 05:31:35 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
12766173	ISSUE.NTF	01/30/2013	SER.125D1

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. SER.125D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Issued	:	February 19, 2013
Patent No.	:	8,377,903
Serial No.	:	12/766,173
Conf. No.	:	1906
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

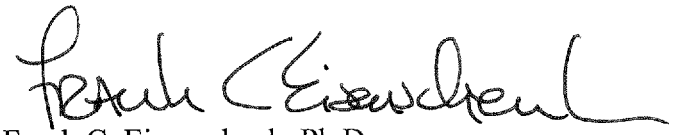
In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 5, line 58: "5217"	Page 8, line 7: --S217--.

A true and correct copy of page 8 of the specification as filed, which supports Applicants' assertion of the error on the part of the Patent Office, accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Eisenschenk
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

FCE/das

Attachments: Certificate of Correction
Page 8 of the specification

in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 1444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,377,903

APPLICATION NO.: 12/766,173

DATED : February 19, 2013

INVENTOR : Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 58, "5217" should read --S217--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Eisenschenk
P.O. Box 142950
Gainesville, FL 32614-2950

Electronic Acknowledgement Receipt

EFS ID:	17237834
Application Number:	12766173
International Application Number:	
Confirmation Number:	1906
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Amanda LaScala
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125D1
Receipt Date:	28-OCT-2013
Filing Date:	23-APR-2010
Time Stamp:	10:02:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	2AO4188.PDF	190990 16f877562ec8c200d33c69bfaf950c3820bc9b0c	no	4

Warnings:

Information:

Total Files Size (in bytes):	190990

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,377,903 B2
APPLICATION NO. : 12/766173
DATED : February 19, 2013
INVENTOR(S) : Giampiero De Luca et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 5,
Line 58, "5217" should read --S217--.

Signed and Sealed this
Twenty-sixth Day of November, 2013

Margaret A. Focarino
Commissioner for Patents of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/25/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
MERCK KGaA and MERCK SERONO SA	ACCORD HEALTHCARE, INC. and INTAS PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,713,947 B2	5/10/2010	Merck Serono SA
2	8,377,903 B2	2/19/2013	Merck Serono SA
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**