



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de propiedad Industrial

División de Nuevas Creaciones

Organización CSA Ltda

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

00-14824

54. TÍTULO Terapia contra el HIV

Nuevo tetra Interferon alfa pegilado en la terapia contra el HIV

51. CLASIFICACIÓN INTERNACIONAL A61K 38121

71. SOLICITANTE Schering corporation

DOMICILIO Kennelworth, Estado de new Jersey, Estados Unidos de America

74. APODERADO

22. BOGOTÁ, D. C.,

⑦



Industria y Comercio
SUPERINTENDENCIA

SOLICITUD
PATENTE DE INVENCION

00-14824

21. **EXPEDIENTE No.**

54. **TITULO** TERAPIA CONTRA EL HIV.

NUEVO TITULO: Interferon Alfa Pegilado en la Terapia contra el HIV.

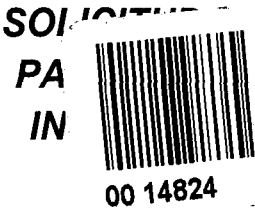
51. **CLASIFICACION INTERNACIONAL** A61K 38/21

71. **SOLICITANTE** SCHERING CORPORATION.

DOMICILIO Kenilworth, Estado de New Jersey, Estados Unidos de América.

74. **APODERADO** CARLOS R. OLARTE

22. **SANTAFE DE BOGOTA, D.C.** MARZO 1, 2000



DATOS DEL SOLICITANTE

(71) Nombres y Apellidos o Razón Social

SCHERING CORPORATION

No. de Identificación

Representante Legal (Persona Jurídica)

País de Domicilio

ESTADOS UNIDOS DE AMERICA.

Departamento o Estado

Estado de New Jersey

Dirección

Kenilworth

Ciudad

Teléfono

(74) DATOS DEL APODERADO

Nombre

CARLOS R. OLARTE

Dirección

CALLE 35 No. 7-25 Piso 4

Ciudad

SANTAFE DE BOGOTÁ

Teléfono

285-14-00/570-0010

DATOS DEL INVENTOR

(72) Nombre del Inventor (es)

MARK A. LAUGHLIN, PAUL W. GLUE, CARLOS O. STANGIS.

Identificación

Dirección

Ciudad

Teléfono

DATOS DE LA PATENTE DE INVENCION

(54) Título de la Invención TERAPIA CONTRA EL HIV.

PRIORIDAD REIVINDICADA

SI ☒

NO ☐

TIPO DE PRIORIDAD

ANDINA ☐

UNIONISTA ☒

(33) País

US

(32) Fecha

Marzo 2, 1999

(31) No. Solicitud

09/260,388

US

Septiembre 9, 1999

09/268,521

US

Abril 8, 1999

09/288,358

US

Diciembre 3, 1999

09/454,004

Para Publicar a los

☐ 6 meses

☐ 12 meses

☒ 18 meses a partir de la fecha de la presente solicitud

(51) CLASIFICACION INTERNACIONAL

2

[illegible]

ANEXOS DE LA SOLICITUD

☒☒

11

11

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☐

or

7

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□

☒☒☒☒

7

7

**SOLICITO LA CONCESION DE LA PATENTE DE INVENCION Y DECLARO
QUE LA INVENCION ES NUEVA Y DE MI PROPIEDAD**



NOMBRE CARLOS R. OLARTE

CC. 79.782.747 de Bogotá

T.P.No. 74.295



Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00014824 00000000
Fecha (AMD): 2000-03-01 17:03:17
Tramite : 002 PATENTES D 1 REGISTRO/ 411 PRESENTAC
Dependencia: 2620 DIVISION DE NUEVAS CREACIONES

Folios: 237

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 00 - 439
FECHA : ENERO 4 DE 2000

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CORREA ORDONEZ	CONSIGNACION	BANCO POPULAR	050-00024-9	871962	04/01/2000	53,815,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	553,000.00
		TOTAL :	\$ 553,000.00

CON: QUINIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE

Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador: 334 12 21
Fax: 281 31 25
Santa Fe de Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

Folios: 237

Radicacion: 00014824 00000000
Fecha (AMD): 2000-03-01 17:03:17
Tramite : 002 PATENTES D 1 REGISTRO/ 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176009-2

CERTIFICACION DE EXCEDENTE : 00 - 6,506
FECHA : ENERO 20 DE 2000

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
AL CORREA ORDOÑEZ	CONSIGNACION	BANCO POPULAR	050-00024-9	874222	20/01/2000	16,575,000.00

***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
RENTISTICO		
50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
	OTROS SERVICIOS ADMINISTRATIVOS	55,000.00
	TOTAL :	55,000.00

SOM: CIENTO Y CINCO MIL PEGOS

FE: CABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No. 27-00 Pisos 5 y 10
Conmutador: 334 12 21
Fax: 281 31 25
Santa Fe de Bogotá, D.C., Colombia

LEA LAS INSTRUCCIONES GENERALES AL RESPALDO DEL BORRADOR DE ESTE FORMULARIO.
RECUERDE QUE TODOS LOS RENGLONES DEBEN ESTAR DILIGENCIADOS CON ALGUN VALOR; EN CASO CONTRARIO, ESCRIBA CERO (0)

891050997815

BANCO COMERCIO
SOC. PARQUE NACIONAL
C1 SET. 24 1990 04
RECIBIDO CON PAGO
41050101074
04
6410601010740 - 1



**DECLARACION Y PAGO
IMPUESTO DE
TIMBRE
NACIONAL**

DATOS GENERALES	1 Administración de Impuestos de: BOGOTA		Código: 03	2 Teléfono: 6102867
	3 Documento de identificación (marque X) C.C. ó T.I. ☒ NIT. ☐ No. 20.194.407		4 Apellidos y Nombres o Razón Social de las partes (máximo 60 caracteres). MARGARITA LLINAS DE GIRALDO	
	5 C.C. ó T.I. ☐ NIT. ☐ No.		6 Apellidos y Nombres o Razón Social de las partes (máximo 60 caracteres). SCHERING CORPORATION	
	7 Dirección (de la persona o entidad identificada en la casilla 4) Cra. 7A No. 94-32		Municipio: BOGOTA	Departamento: CUNDINAMARCA
			8 Número documentos UNO	
9 Relación el(los) tipo(s) de documento(s), indicando número, fecha, valor y naturaleza de la transacción TRADUCCION OFICIAL No. 1682 de autenticaciones notariales y subsiguientes correspondientes a un Poder suscrito por Schering Corporation y firmado por el señor Stainar V. Kanstad, Director Patentes Internacionales de dicha Compañía, efectuada el 21 de septiembre de 1.990.- - - - - - - - - - Septiembre 24/1.990.-				

FIRMA

Responsable del pago:

Nombre: _____

C.C. No.: _____

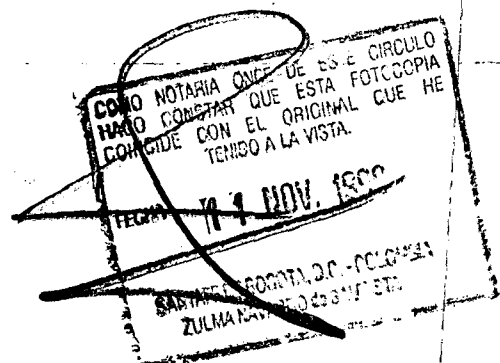
PAGO EN BANCOS	1 VALOR DEL IMPUESTO A PAGAR	VP	600
	2 Sanciones	VS	-0-
	3 Intereses de mora	IM	-0-
	4 TOTAL A PAGAR (renglones 1 + 2 + 3)	TP	600
FORMA	Efectivo ☒ Cheque ☐ No.		
	Código Banco		

021601* 240950
0000 1-620
4125 *600.00

DEM-31-DX-80

CONTRIBUYENTE

MH 1000/80



6
TRADUCCION OFICIAL No. 1682 de un documento escrito en Ingles.

Esta es una Traducción efectuada el día 21 de Septiembre de 1990 por la Sra. Margarita de Giraldo, c.c. 20.194.407 de Bogotá. Traductora e Interprete Oficial según Resolución No. 7899 del Ministerio de Justicia de Colombia.

Autenticaciones Notariales y subsiguientes correspondientes a un Poder suscrito por SCHERING CORPORATION y firmado por el Sr. STEINAR V. KANSTAD, Director Patentes Internacionales de dicha Compañia.

Declaración Notarial expedida el día 25 de Julio de 1990 autenticando la firma y cargo del Sr. Steinar V. Kanstad como Director Patentes Internacionales de SCHERING CORPORATION. Firmada: GERTRUDE P. RUDNICK, Notario Público cuyo cargo expira el día 16 de Marzo de 1994. Firma y sello del Notario.

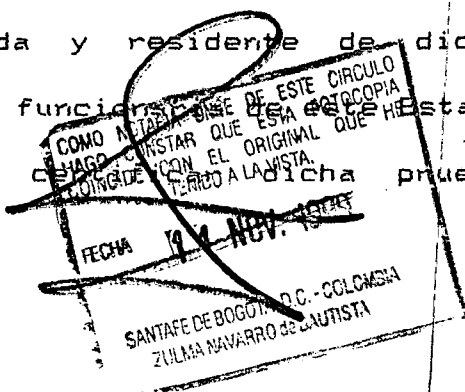
El Poder y la Declaración Notarial arriba mencionados no se traducen por estar escritos en Español.

ESTADO DE NEW JERSEY

CONDADO DE MORRIS

A SABER:

Yo, ALFONSE W. SCERBO, Escribano del Condado de Morris y Escribano Delegado del Tribunal Superior, en y para dicho Condado, Tribunal este de Registro, por medio del presente certifico que la Notario indicada en el anterior instrumento y quien recibió la anterior prueba, reconocimiento o declaración y certificó el mismo, desempeñaba el cargo de NOTARIO PUBLICO debidamente comisionada, juramentada y residente de dichos Condado y Estado y que como tal funcionaria en este Estado, estaba autorizada para recibir y certificar la copia de la prueba,



Margarita de Giraldo
MARGARITA DE GIRALDO
TRADUCTORA OFICIAL
RESOLUCION 7899 DEL
MINISTERIO DE JUSTICIA

reconocimiento o declaración, así como para recibir y certificar pruebas de reconocimiento de escrituras para el traspaso de terrenos, herencias o bienes por heredar y otros instrumentos escritos que deban registrarse en dicho Estado; certifico además que se debe dar total fe y credito a todos sus actos oficiales y que estoy familiarizado con la escritura y caligrafía de dicha Notario y creo, en conciencia, que la firma que aparece en el instrumento al cual se adjunta el anterior certificado es su firma autentica.

GERTRUDE P. RUONICK (Notario)

EN TESTIMONIO DE LO CUAL, suscribo mi firma y estampo el sello de dichos Tribunal y Condado en Morristown.

Fecha: Agosto 7 de 1990.

ALFONSE W. SCERBO - Escribano

Firmado: ANTOINETTE MENNELLE - Escribano Delegado Especial.

EN ESPAÑOL: La legalización de las firmas anteriores inclusive por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 263677 del día 18 de Septiembre de 1990.

ES TRADUCCION FIEL Y COMPLETA DE LA CUAL SE DEJA COPIA EN ESTOS ARCHIVOS PARA SU CONFRONTACION.

Margarita Llinas de Giraldo
MARGARITA LLINAS DE GIRALDO
TRADUCTORA OFICIAL
RESOLUCION 7899 DEL
MINISTERIO DE JUSTICIA

Margarita Llinas de Giraldo
MARGARITA LLINAS DE GIRALDO
c.c. 20.194
Traductora Oficial
según Resolución No. 7899 del
Ministerio de Justicia

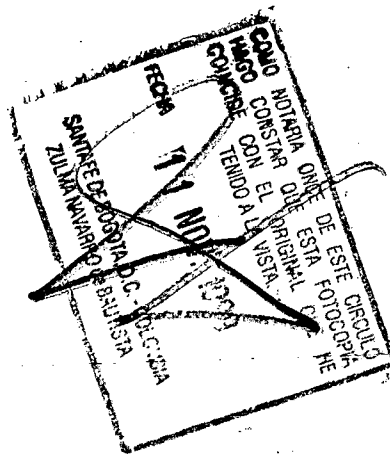
COM NOTARIO
HABER CONSTATADO EL ORIGINAL
CONFEEREN EN BOGOTÁ
TENDIENDO FECHA
SANTAFÉ DE BOGOTÁ
JANUARI 1990

160350

NO SE ASUME.
RESPONSABILIDAD DEL TEXTO

97 JUL -9 AM 9 04

JEFE DE LEGALIZACIONES
SANTAFÉ DE BOGOTÁ D.C.





CONSULADO GENERAL DE COLOMBIA

10 EAST 46TH STREET
NUEVA YORK, N.Y. 10017

TEL. 949-9898

263877

EL SUSCRITO CONSUL DE COLOMBIA,

VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS

MANIFIESTA EL PODER
SECCION NEGOCIOS

HACE CONSTAR:

Cuya firma aparece al pie del
presente documento, desempeñaba
en esa fecha las funciones allí
indicadas.

BOGOTA, 18 SET 1990

JOSE ANGEL ALDANA
JEFE NEGOCIOS GENERALES

CERTIFICA:

Que ante la Oficina del County Clerk (SPECIAL DEPUTY) ANTOINETTE
de la Corte Suprema del Estado de NEW JERSEY
se encuentra debidamente registrado el señor GERTRUDE P. RUDNICK
como Notario del Estado de NEW JERSEY y ante quien
se AUTENTICO LA FIRMA DEL SIGNATARIO DEL PRESENTE PODER.

Que la compañía SCHERING CORPORATION
es una sociedad constituida de acuerdo con las leyes del Estado de NEW JERSEY
ESTADOS UNIDOS DE AMERICA y cumple su objetivo conforme a las mismas.

Que el señor STEINAR V. KANSTAD
quien en su carácter de DIRECTOR, PATENTES INTERNACIONALES
de la citada compañía, confiere EL PODER PRECEDENTE, cuya firma fue autenticada ante
Notario, es su representante legal.

EL CONSUL NO ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO.
Este Certificado se expide en Nueva York, Estados Unidos de América, a los 24 días
del mes de AGOSTO de 1990

PAGADO IMPUESTO DE TIMBRE
VALOR US\$6.00 (SEIS DOLARES).
NUEVA YORK



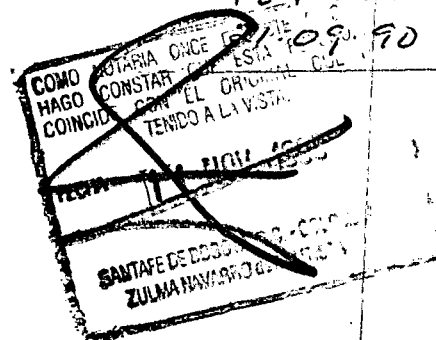
24

J. Alzamora
Joaquín Alfredo Alzamora Campo
Cónsul

MARGARITA LINAS DE GIRALDO
TRADUCTORA OFICIAL
RESOLUCION 744 DEL
MINISTERIO DE JUSTICIA

T.O. #1682

109.90



Members of the Firm

BAKER & MCKENZIE

APARTADO AEREO 3746

BOGOTA, COLOMBIA

POWER OF ATTORNEY

The undersigned,

SCHERING CORPORATION

located in

Kenilworth, New Jersey
United States of America

declares that it hereby grants to

JAMES W.F. RAISBECK and/or
ROBERT B. RAISBECK and/or
ALVARO CORREA-ORDONEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of: registrations of letters patents, extensions, assignments, changes of name, changes of address, filing and prosecution of oppositions, registration of industrial models.

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the marks, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in Madison, New Jersey,
U.S.A.

on the 25th day of July

19 90.

SCHERING CORPORATION

By:

Steinar V. Kanstad
Director, International Patents

PODER

La abajo firmada

SCHERING CORPORATION

domiciliada en

Kenilworth, New Jersey
Estados Unidos de América

declara por el presente otorgar a

JAMES W.F. RAISBECK y/o
ROBERT B. RAISBECK y/o
ALVARO CORREA-ORDONEZ,

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de: registro de patentes, extensiones, traspasos, cambios de nombre, cambios de dirección, presentación y tramitación de oposiciones, registro de modelos industriales

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de las marcas se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en Madison, New Jersey
E.U.A.

a los 25

19 90



BAKER & MCKENZIE

ATTORNEYS AT LAW

APARTADO AEREO 3746

BOGOTA, COLOMBIA

NOTARIAL CERTIFICATION

On this 25th day of July, 1990

~~1988~~ the undersigned Notary

CERTIFIES

1. That Steinar V. Kanstad

of legal age and domiciled in Madison,
New Jersey, U.S.A.

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she
has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Director, International Patents
of the juridical person

SCHERING CORPORATION

4. That the juridical person

SCHERING CORPORATION

having its home office in 2000 Galloping Hill Road,
Kenilworth, New Jersey 07033, U.S.A.

is duly organized, has present legal existence and that the
purposes for which the power of attorney is granted are within
the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that
his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the
following authentic documents for such purpose exhibited to
me and which I mention specifically, giving their dates and
their origin or source:

Power of Attorney from SCHERING
CORPORATION, dated September 12,
1979.

Gertrude P. Rudwick

GERTRUDE Notary Public
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Mar. 16, 1994
Registered in Middlesex and Morris Counties

CERTIFICACION NOTARIAL

A los 25 días del mes de julio

1990

de ~~1988~~, el suscrito Notario

DA FE

1. Que Steinar V. Kanstad

mayor y domiciliado en Madison, New Jersey
E.U.A.

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para
el otorgamiento.

3. Que el otorgante ha suscrito el referido documento en su
carácter de Director Internacional de
Patentes
de la persona jurídica

SCHERING CORPORATION

4. Que la persona jurídica

SCHERING CORPORATION

con sede en 2000 Galloping Hill Road,
Kenilworth, New Jersey 07033

está legalmente constituida, que tiene existencia legal actual y
que el acto para el cual se ha otorgado el poder está comprendido
entre los que constituyen su objeto social. EU

5. Que el otorgante tiene efectivamente la representación que
ostenta, y que esta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los
siguientes documentos auténticos que al efecto se me exhibieron
y que menciono específicamente con expresión de sus fechas y
de su origen o procedencia:

Poder de Schering Corporation, de
fecha septiembre 12 de 1979.



11

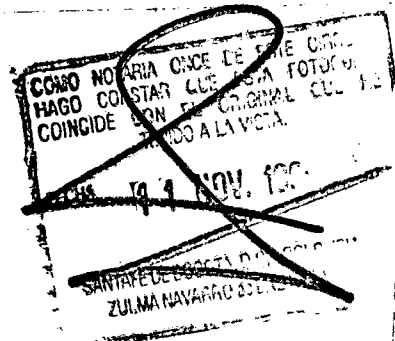
of NEW JERSEY - COUNTY of MORRIS ss. I, ALFONSE W. SCERBO, Clerk of the County of Morris and Deputy of the Superior Court, holden in and for said County, the same being a Court of Record, do hereby certify the Notary set forth by whom the foregoing proof, acknowledgment or affidavit taken and certified was at the time of taking proof, acknowledgment or affidavit a **Notary Public**, duly commissioned, sworn and residing in said County and State, as as officer of this State, authorized to take and certify said proof, acknowledgment or affidavit as well as to take and certify proofs of acknowledgments of deeds for conveyance of lands, tenements or hereditaments and other instruments in Writing, to be recorded in said State; and full faith and credit are and ought to be given to his official acts and I am well acquainted with the handwriting of said Notary and believe the signature to the instrument to which the certificate is attached is his genuine signature.

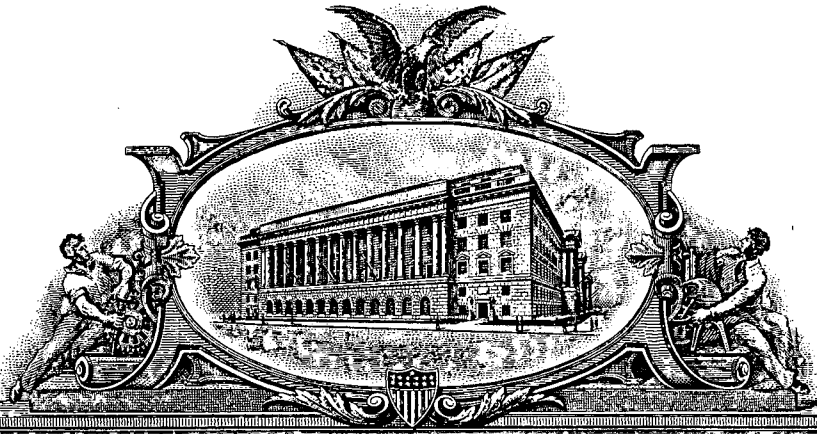
--- Gertrude P. Rudnick --- (Notary)

In Testimony Whereof, I have set my hand and affixed the seal of said Court and County at Morristown:

Dated: August 2, 1990 Alfonse W. Scerbo Clerk

Antoinette Menzelle Special Deputy Clerk





THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 04, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/260,388

FILING DATE: March 02, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

**P. SWAIN
Certifying Officer**

03/02/99

jc639 U.S. PTO

A 13

PATENT

Attorney Docket No.: IN01003

Box Patent Application
ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

jc549 U.S. PTO
09/260388
03/02/99

Sir:

Transmitted herewith for filing is the patent application, including a specification and claim(s), of:

First Named Inventor:

Title: HIV THERAPY

Also enclosed are items 1-6, as checked:

1. ☐ _____ sheets of drawing(s).
2. ☒ Declaration and Power of Attorney (3 pages).
 - a. ☒ Newly executed.
 - b. ☐ Copy from a prior application (box no. 10 below also completed).
 - (i). ☐ A signed statement is enclosed deleting inventor(s) named in the prior application.
 - (ii). ☐ The entire disclosure of the prior application, from which a copy of the declaration is supplied, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
3. ☐ A floppy disk, including the computer form of the Sequence Listing in the specification. The undersigned certifies that the computer form is equivalent in content to the Sequence Listing in the specification.
4. ☐ A preliminary amendment.
5. ☐ An information Disclosure Statement (PTO Form 1449) with copies of _____ cited documents.
6. ☐ _____
7. ☒ The filing fee is as follows, calculated after entry of any preliminary amendment:

For	Number Filed (1)	Number Extra (2)	Rate	Fee
Basic Fee				\$760.00
Total Claims	31- 20 =	(10)	x \$18.00	\$198.00
Independent Claims	4- 3 =	(1)	x \$78.00	\$78.00
Multiple Dependent Claims				\$0.00
			TOTAL FILING FEE	\$1036.00

*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

14

8. ☒ The Commissioner is authorized to charge Deposit Account No. 19-0365 in the amount of the above Total Filing Fee. A duplicate of this form is enclosed for fee processing.

9. ☒ General Authorization. This paper constitutes a general authorization to the Commissioner, for any deficiency in the above Total Filing Fee and all fee requirements subsequent to the instant filing, to charge all fees for amendments, petitions, and any and all other papers to our Deposit Account 19-0365. This is not, however, an automatic authorization to charge our Deposit Account for the Issue Fee.

10. ☐ This application is a request for filing a ☐ Continuation ☐ Divisional ☐ Continuation -in-part of prior application Serial No.: _____ filed on _____

Thomas D. Hoffman 3/2/99
Thomas D. Hoffman
Attorney/Agent for Applicants
Reg. No.: 28221
SCHERING-PLOUGH CORPORATION
Patent Dept. K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone: (908) 298-5037
Facsimile: (908) 298-5388

EXPRESS MAIL label no.: EL226882475US

Date of Deposit: March 2, 1999

Rev. 3/99 ss

HIV THERAPY

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating patients having immunodeficiency virus type-1 ("HIV-1") infections by administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-1-RNA .

A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART") ; HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naive patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

The present invention provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-RNA.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week, followed by (2) administering, in a second treatment time period, a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

DETAILED DESCRIPTION

The present method of treating patients having HIV-1 infections comprises administering a therapeutically effective amount of pegylated interferon-alfa as monotherapy or in association with a therapeutically effective amount of anti-HIV-1 therapy, especially HAART in accordance good clinical practice to minimize detectable HIV-RNA serum levels. See for example A-M. Vandamme et al., in Antiviral Chemistry & Chemotherapy, 9:187-203 (1998). The initiation of the HAART may occur before, after or concurrently with administering a therapeutically effective amount of pegylated interferon-alfa in accordance with the present invention. In a preferred embodiment of the present invention, the method of treating patients having HIV-1 infections comprises two treatment time periods. In the first treatment time period, a therapeutically effective

amount of pegylated interferon-alfa is administered for a first treatment time period sufficient to lower detectable HIV-1-RNA serum levels, preferably by a power of 10, more preferably by at least two powers of ten, i.e., at least 10^2 , lower than the initial HIV-1-RNA serum level. In the second treatment time period, the method entails continuing the administration of a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of HAART in accordance good clinical practice to minimize detectable HIV-RNA serum levels. A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections, including when to start multidrug therapy and which drugs to combine. The triple drug therapy may include two NRTIs and one PI, but there are many issues to be considered in the choice of the precise HAART for any patient. See for example, Tables 3 & 2 and Figure 2 in A-M. Vandamme et al., listed hereinabove.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), preferably about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week, and most preferably about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 200 micrograms to about 250 micrograms

QW for at least two to four weeks, and the therapeutically effective amount of pegylated interferon alfa-2a administered in the second treatment time period in association with a therapeutically effective amount of HAART is in the range of about 50 micrograms to about 500 micrograms once a week, preferably about 200 micrograms to about 250 micrograms once a week

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered is in the range of about 50 micrograms to about 500 micrograms once a week, preferably about 200 micrograms to about 250 micrograms QW.

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG₁₂₀₀₀-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG₁₂₀₀₀-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG₁₂₀₀₀-interferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG₁₂₀₀₀ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG₁₂₀₀₀ attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to

improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

The term "interferon-alfa" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alfa-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-

based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0510 356 and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human serum albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosal, cresol or benylalcohol), and surfactants (e.g. tween or polysorbates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

The term "patients having HIV-1 infections" as used herein means any patient having HIV-1 infection and includes treatment-naive patients as well as treatment-experienced patients.

The term "treatment-naive patients" as used herein means patients with HIV-1 who have never been treated with any antiviral drugs, e.g., NRTI, NNRTI, PI or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

The term "treatment-experienced patients as used herein means those patients who have initiated some form of anti HIV therapy including, but not limited to HAART.

In a preferred embodiment of the present invention, pegylated interferon alfa is administered to HIV-1 infected patients prior to initiation of HAART, and preferably about two to about four weeks prior to initiation of HAART. In another preferred embodiment of the present invention, administration of pegylated interferon alfa is initiated concurrently, i.e., on the same day with the administration of HAART.

HAART is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose is administered during the same period of time that the patient receives doses of HAART. Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage

form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnostics) or of Nuclisens HIV-1 QT -1. This methodology is described by Schooley, RT, Antiviral Therapy(1997), 2 (Suppl. 4):59-70 .

The following clinical protocol may be used to administer the HIV-1 therapy of the present invention:

The study population will include male and female patients with newly diagnosed HIV-1 infection who are treatment naive and will be included if they meet the following inclusion and exclusion criteria:

Subject Inclusion Criteria:

- Subjects between the ages of 18 and 55 years, diagnosed with HIV-1 infection who are treatment naive.
- HIV-RNA by Amplicor test, Version 1.5 of greater than 5,000 copies/mL at both screening samples.
- CD₄⁺ count greater than 200 cells/mL.

- Subjects in good physical health with clinically acceptable safety laboratory test results and *clinically acceptable* ECG.
- Absence of active systemic opportunistic infection on physical examination and screening chest x-ray.
- No history of systemic opportunistic infection or immunization within the preceding 2 months.
- The following laboratory parameters must be met:
 - ◆ Platelet count $\geq 100,00/mL$ ($75 \times 10^9/L$)
 - ◆ Hemoglobin ≥ 9 gm/dL (90 gm/L)
 - ◆ Absolute neutrophil count $\geq 1500/\mu L$ ($0.75 \times 10^9/L$)
 - ◆ Creatinine < 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT ≤ 5 x upper limit of normal
 - ◆ Bilirubin ≤ 2.5 x upper limit of normal
- A negative urine pregnancy test (females only)
- Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.
- Subject Inclusion Criteria
- Subjects with previous IFN or anti-retroviral therapy for treatment for HIV-1.
- Subjects with clinically significant disorders not related to their HIV disease.
- Progression of HIV-1 to AIDS.
- Females who are breast-feeding or pregnant or who are not using adequate birth control.
- Individuals who have participated in a clinical trial of an investigational drug in the previous 3 months.
- Subjects who are positive for hepatitis B surface antigen or hepatitis C antibody.

- Subject with allergy to E. coli proteins, *or any clinically significant hypersensitivity to other drugs..*
- Subjects with a significant past medical/psychiatric history, specifically depression or dementia.
- Presence of Interferon neutralizing antibodies (these antibodies (these results may not be available during screening; patients will be considered for inclusion without these results. Patients who are enrolled who are subsequently found to be positive for Interferon neutralizing antibodies will be removed from the study and replaced.

The subjects will be randomized to receive pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b at doses of 0.5, 1.0, 1.5 or 3.0 micrograms per kilogram by subcutaneous injection once a week for at least 4 weeks. On day 28 of the treatment, the fifth subcutaneous injection of PEG₁₂₀₀₀-interferon alfa 2b will be given in association with HAART. HAART may also be initiated before or concurrently with the administration of the pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b

Overall Design and Plan of the Study

Efficacy

The primary efficacy objective will be lowering of the HIV-1-RNA serum levels by a factor of 10 or greater

Serum HIV-1-RNA/qPCR testing will be performed by a central laboratory. A positive HIV-1-RNA assay result will be required at Baseline; only patients positive for HIV-1-RNA will be eligible to participate..

We claim:

1. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower detectable HIV-1-RNA.
2. The method of claim 1, wherein the patients are treatment-naive patients.
3. The method of claim 1, wherein the patients are treatment-experienced patients.
4. The method of claim 1, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.
5. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.
6. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram QW.
7. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.

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8. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b is administered in association with HAART.

9. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.

10. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms QW.

11. A method of treating patients having HIV-1 infections which comprises administering about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

12. . The method of claim 11, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.

13. The method of claim 11, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective amount of HAART.

14. The method of claim 11, wherein the pegylated interferon-alfa-2b is administered prior to administering a therapeutically effective amount of HAART.

15. The method of claim 11, wherein the pegylated interferon-alfa-2b is administered QW for at least about 2 to 4 weeks prior to administering a therapeutically effective amount of HAART.

16. The method of claim 11, wherein the pegylated interferon-alfa-2b is administered after administering a therapeutically effective amount of HAART.

17. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa.

18. The method of claim 17, wherein the patients are treatment-naive patients.

19. The method of claim 17, wherein the patients are treatment-experienced patients.

20. The method of claim 17, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.

21. The method of claim 17, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.

22. The method of claim 17, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of

pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram QW.

23. . The method of claim 17, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.

24. The method of claim 17, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.

25. The method of claim 17, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms QW.

26. A method of treating patients having HIV-1 infections which comprises (1) administering in a first treatment time period of at least about two to about four weeks about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week , followed by (2) administering in a second treatment time period, a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa-2b once a week

27. The method of claim 26, wherein about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

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29.. The method of claim 26, wherein about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

30. The method of claim 26, wherein the patients are treatment-naïve patients.

31. The method of claim 26, wherein the patients are treatment-experienced patients.

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DECLARATION AND POWER OF
ATTORNEY FOR PATENT APPLICATION

Attorney's Docket No. IN01003

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

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

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

HIV THERAPY

the specification of which

☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____

and was amended on _____ (if applicable).

☐ was filed on _____ as PCT International Application No. _____

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

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Priority Claimed

(Number)	(Country)	(Day/Month/Year Filed)	Yes or No
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I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(Application Number)	(Filing Date)
----------------------	---------------

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)
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Power of Attorney: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in Patent and Trademark Office connected therewith. (List name and registration number.)

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 04, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/268,521

FILING DATE: March 12, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

N. Woodson
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Certifying Officer

03/12/99
JCS98 U.S. PTO

PATENT

Attorney Docket No.: IN01003K

JC135 U.S. PTO
09/268521
03/12/99

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Box Patent Application
ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application, including a specification and claim(s), of:

Inventors: Mark A. Laughlin, Paul W. Glue and Carlos O. Stalgis

Title: HIV THERAPY

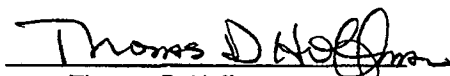
Also enclosed are items 1-6, as checked:

- 1. ☐ _____ sheets of drawing(s).
- 2. ☒ Declaration and Power of Attorney (3 pages).
 - a. ☐ Newly executed.
 - b. ☐ Copy from a prior application (box no. 10 below also completed).
 - (i). ☐ A signed statement is enclosed deleting inventor(s) named in the prior application.
 - (ii). ☐ The entire disclosure of the prior application, from which a copy of the declaration is supplied, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
- 3. ☐ A floppy disk, including the computer form of the Sequence Listing in the specification. The undersigned certifies that the computer form is equivalent in content to the Sequence Listing in the specification.
- 4. ☐ A preliminary amendment.
- 5. ☐ An information Disclosure Statement (PTO Form 1449) with copies of _____ cited documents.
- 6. ☐ _____
- 7. ☒ The filing fee is as follows, calculated after entry of any preliminary amendment:

For	Number Filed (1)	Number Extra (2)	Rate	Fee
Basic Fee				\$760.00
Total Claims	47- 20 =	(27)	x \$18.00	\$486.00
Independent Claims	4- 3 =	(1)	x \$78.00	\$78.00
Multiple Dependent Claims				\$0.00
			TOTAL FILING FEE	\$1324.00

*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

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8. ☒ The Commissioner is authorized to charge Deposit Account No. 19-0365 in the amount of the above Total Filing Fee. A duplicate of this form is enclosed for fee processing.
9. ☒ General Authorization. This paper constitutes a general authorization to the Commissioner, for any deficiency in the above Total Filing Fee and all fee requirements subsequent to the instant filing, to charge all fees for amendments, petitions, and any and all other papers to our Deposit Account 19-0365. This is not, however, an automatic authorization to charge our Deposit Account for the Issue Fee.
10. ☒ This application is a request for filing a ☐ Continuation ☐ Divisional ☒ Continuation -in-part of prior application Serial No.: (ATTORNEY DOCKET # IN01003 filed on March 2, 1999)



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Date of Deposit: March 12, 1999

Rev. 3/99 ss

PATENT CASE

IN01003K

HIV THERAPY

CROSS-REFERENCE TO RELATED APPLICATION: This application is a continuation-in-part of commonly-owned U.S. Patent Application SN (Atty. Docket # IN01003), filed by March 2, 1999.

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating patients having immunodeficiency virus type-1 ("HIV-1") infections by administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-1-RNA .

A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART") ; HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naive patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

The present invention provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-RNA.

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The present invention also provides a method of treating patients having HIV-1 infections which comprises administering about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 therapy in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week, followed by (2) administering, in a second treatment time period, a therapeutically effective amount of an anti-HIV-1 therapy in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week, followed by (2) administering, in a second treatment time period, a

therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.

DETAILED DESCRIPTION

The present method of treating patients having HIV-1 infections comprises administering a therapeutically effective amount of pegylated interferon-alfa as monotherapy or in association with a therapeutically effective amount of at least one of ribavirin, interleukin-2("IL-2"), interleukin-12(" IL-12"), and pentafuside alone or in combination with an anti-HIV-1 therapy, especially, HAART in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. See for example A-M. Vandamme et al., in Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) and "Drugs for HIV Infection" in The Medical Letter Vol. 39 (Issue 1015) December 5, 1997, pages 111-116.. The initiation of the HAART may occur before, after or concurrently with administering a therapeutically effective amount of pegylated interferon-alfa in accordance with the present invention. In a preferred embodiment of the present invention, the method of treating patients having HIV-1 infections comprises two treatment time periods. In the first treatment time period, a therapeutically effective amount of pegylated interferon-alfa is administered for a first treatment time period sufficient to lower HIV-1-RNA plasma levels, preferably by a power of 10, more preferably by at least two powers of ten, i.e., at least 10^2 , lower than the initial HIV-1-RNA plasma level. In the second treatment time period, the method entails continuing the administration of a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of HAART in accordance with good clinical practice to minimize

HIV-1-RNA plasma levels . A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections, including when to start multidrug therapy and which drugs to combine. The triple drug therapy may include two NRTIs and one PI, but there are many issues to be considered in the choice of the precise HAART for any patient. See for example, Tables 1 & 2 and Figure 2 in A-M. Vandamme et al., listed hereinabove.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), preferably about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week, and most preferably about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 200 micrograms to about 250 micrograms QW for at least two to four weeks, and the therapeutically effective amount of pegylated interferon alfa-2a administered in the second treatment time period in association with a therapeutically effective amount of HAART is in the range of about 50 micrograms to about 500 micrograms once a week, preferably about 200 micrograms to about 250 micrograms once a week.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated

interferon alfa-2a administered is in the range of about 50 micrograms to about 500 micrograms once a week, preferably about 200 micrograms to about 250 micrograms QW.

Ribavirin is administered to the patient in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of ribavirin. The amount of ribavirin administered concurrently with the pegylated interferon-alfa is from about 400 to about 1600 mg per day, preferably about 600 to about 1200 mg/day or about 800 to about 1200 mg day and most preferably about 1000 to about 1200 mg/kg a day.

When the ribavirin is administered to the patient before the pegylated interferon-alfa is administered, the amount of ribavirin administered in the first treatment time period is from 400 to 1600 mg per day, preferably 600 to 1200 mg/day or about 800 to 1200 mg day and most preferably about 1000 to 1200 mg/kg a day. The amount of ribavirin administered in the second treatment time period is in the range of from about 800 to 1200 mg per day, preferably from about 1000 to 1200 mg per day.

Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Ribavirin may be administered orally in capsule or tablet form in association with the parenteral administration of pegylated interferon-alfa. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work

so long as the proper dosages are delivered without destroying the active ingredient.

The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NTRI" s) as used herein means nucleosides and nucleotides and analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HIVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709;; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN trademark from Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON tradename from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Laval, Quebec H7V, 4A7, Canada; emitricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4(also called beta-L-D4C and named beta-L-2', 3'-dicleoxy-5-fluorocytidene) licensed by Yale University to Vion Pharmaceuticals, New

Haven CT 06511; and DAPD, the purine nucleoside, (-)-beta-D-2,6,-diaminopurine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707 and Iodenosine (FddA), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, a acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohoken, PA. 19428.

The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

Typical suitable non-nucleoside reverse transcriptase inhibitors include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delaviradine (BHAP, U-90152) available under the RESCRIPTOR tradename from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename from DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, a furopyridine-thiopyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5- (3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707 and (+)-calanolide A (NSC-675451) and B are coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697

licensed to Med Chem Research which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN (available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

Typical suitable protease inhibitors include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOUASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfinavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; amprenavir (141W94), a non-peptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543 as a 2nd-generation HIV-1 PI; ABT-378 under development by Abbott, Abbott Park, IL 60064; and Yissum Project No. 11607, a

synthetic protein based on the HIV -1 Vif protein under preclinical development by Yissum Research Development Co., Jerusalem 91042 , Israel; AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; and lobucavir [(-)-BCHG, BMS-180194] disclosed in EP-0358154 and under development by Bristol-Myers Squibb, Princeton, NJ 08543.

The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the triple and quadruple combination therapies called HAART.

Typical suitable anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from , NNRTIs and PIs ;see Talbes I, II and III, hereinafter.

Typical suitable HAART - multidrug combination therapies- include (a) triple combination therapies such as two NRTIs and one PI ; or (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment-naïve patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is preferred unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺ and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug, e.g., one PI or one NNRTI could be added. See the Table A hereinbelow.

Table A**ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES****A. Triple Combination Therapies**

1. Two NRTIs¹ + one PI²
2. Two NRTIs¹ + one NNRTI³

B. Quadruple Combination Therapies⁴

Two NRTIs + one PI + a second PI or one NNRTI

C. ALTERNATIVES:⁵

Two NRTI¹

One NRTI⁵ + one PI²

Two PIs⁶ ± one NRTI⁷ or NNRTI³

One PI² + one NRTI⁷ + one NNRTI³

FOOTNOTES TO TABLE A

1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine; See also Table I
2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules.
Ritonavir is used less frequently because of troublesome adverse effects. The old formulation of saquinavir was used least often because of its poor bioavailability and limited effectiveness, but the new formulation should be more effective See also Table III
3. Nevirapine or delavirdine. See also Table II
4. See A-M. Vandamme et al Antiviral Chemistry + Chemotherapy 9:187 at p 193-197 and Figures 1 + 2.
5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or

toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV-resistance and clinical failure in many patients.

6. Most data obtained with saquinavir and ritonavir (each 400 mg bid). See also Table III
7. Zidovudine, stavudine or didanosine. See also Table I

Other anti-HIV-1 drugs found useful for administration in association with pegylated interferon alfa include hydroxyurea, ribavirin, IL-2 and IL-12. These above-listed anti-HIV-1 drugs may also be administered in association with pegylated interferon alfa in association with any anti-HIV-1 drug therapy, especially the triple and quadruple drug combinations called HAART.

Hydroxyurea (Droxia) is a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells. Hydroxyurea discovered at the NCI is under development by Bristol-Myers Squibb. In preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine.

The pegylated interferon alfa, PEG₁₂₀₀₀-IFN-alfa2b (available from Schering-Plough Research Institute, Kenilworth, NJ) increased the in vitro anti HIV-1 activity of ribavirin. The combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited HIV replication in vitro using phytohemagglutinin ("PHA" - P) - activated peripheral blood mononuclear cells ("PBMCs") at doses corresponding to plasmatic concentrations observed in animals and man. Healthy PBMCs were separated from a buffy-coat of one HIV-seronegative blood donor by Ficoll-Hypaque density gradient centrifugation. PBMCs were activated by 1 µg/ml phytohemagglutinin (PHA-P) for two days in cell culture medium A: RPMI

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1640 supplemented with 10% heat-inactivated (+56°C, 45 min.) fetal calf plasma (FCS), 2 mM L-glutamine and a tri-antibiotic mixture 1X (penicillin, streptomycin, neomycin; PSN). After these two days, cells were washed and cultured at one million cell per milliliter in cell culture medium B: cell culture medium A supplemented with 20 IU/ml recombinant human interleukin-2. Cells were maintained at +37°C in a 5% CO₂-air humidified atmosphere. Experiments were repeated twice with cells of other blood donors. In total, three independent experiments were performed.

PBMCs were infected with 1,000 50% Tissue Culture Infectious Doses (TCID₅₀) of the reference HIV-1-LAI strain [F.Barre'-Sinoussi, Science, 1983, 220, 868-871]. This strain has been amplified using PHA-P-activated umbilical blood mononuclear cells (UBMC). Viral stock has been then titrated on PHA-P activated PBMC by end-point dilution. TCID₅₀ was then calculated using Karber's formula [Arch. Exp. Path. Pharmacol., 1931, 162, 126-133].

PEG₁₂₀₀₀-IFN-α2b and ribavirin, alone and in combination, and AZT used as a control, were administrated 24 hours before HIV-1 infection and maintained all along the culture. Three doses of PEG₁₂₀₀₀-IFN-α2b and ribavirin were used.

200,000 PHA-P-activated PBMCs were added to each well of 96-well microplates. Cells were 24 hour-pretreated prior to infection with the reference HIV-1-LAI strain. Twice a week, cell supernatants were collected, and drugs and medium were renewed. At day 7, RT activity were determined in cell supernatants, and potential cytotoxic effects of drugs and drug combinations were evaluated by microscopic observation.

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Viral replication was measured by determining reverse transcriptase ("RT") activity in cell supernatants using Retro-Sys® kit, according to manufacturer's recommendations (Innovagen, Lund, Sweden).

Effective doses were calculated using cumulative RT activities with Chou J. and TC. microcomputer software.

The combined effects were analyzed using either the combination index (CI) [Chou & Talalay, 1984] with J and TC Chou microcomputer software, or the fractionary inhibitory concentration (FIC) index [Antimicrob. Agents. Chemother., 1987, 31, 1613-1617]. When the CI or FIC index is equal to 1, the combination is additive. When it is below 1.0, the combination is synergistic, and when it is above 1.0, the combination is judged as antagonistic.

PEG₁₂₀₀₀-IFN-alfa2b as well as the combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited the HIV replication at doses corresponding to plasmatic concentrations measured in mice and HIV-1 infected patients [BE. Gilbert, et al. Antimicrob. Agents Chemother., 1988, 32, 117-121; E. Connor et al., Antimicrob. Agents Chemother., 1993, 37, 537-539].

IL-2 is disclosed in Ajinomoto EP-0142268, Takeda EP-0176299, and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314 is available under the PROLEUKIN(aldesleukin) tradename from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration

upon reconstitution and dilution with water; doses of about 1 to about 20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred.

IL-12 is disclosed in WO96/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 microgram/kg/day, sc.

Pentafuside (DP-178, T-20) a 36-amino acid synthetic peptide, disclosed in U.S. Patent No. 5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc infusion or injection together with efavirenz and 2 PI's to HIV-1 positive patients refractory to a triple combination therapy; use of 100 mg/day is preferred.

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG₁₂₀₀₀-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG₁₂₀₀₀-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG₁₂₀₀₀-interferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN

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alfa-2b molecule. A single PEG₁₂₀₀₀ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG₁₂₀₀₀ attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

The term "interferon-alfa" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0510 356 and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human plasma albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosal, cresol or benylalcohol), and surfactants(e.g. tween or polysorbates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo

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Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

The term "patients having HIV-1 infections" as used herein means any patient having HIV-1 infection and includes treatment-naive patients as well as treatment-experienced patients.

The term "treatment-naive patients" as used herein means patients with HIV-1 who have never been treated with any antiretroviral drugs, e.g., NRTI, NNRTI, PI or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

The term "treatment-experienced" patients as used herein means those patients who have initiated some form of anti HIV therapy including, but not limited to HAART.

HAART is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose may be administered before, after or during the same period of time that the patient receives doses of HAART.

In a preferred embodiment of the present invention, pegylated interferon alfa is administered to HIV-1 infected patients prior to initiation of HAART, and preferably about two to about four weeks prior to initiation of HAART. In another preferred embodiment of the present invention, administration of pegylated interferon alfa is initiated concurrently, i.e., on the same day with the administration of HAART. In another preferred embodiment of the present invention the pegylated interferon-alfa is administered after the HIV-1 infected patient has initiated HAART.

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Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnostics) or of Nuclisens HIV-1 QT -1. This methodology is described by Schooley, RT, Antiviral Therapy(1997), 2 (Suppl. 4):59-70 .

The doses and dosage regimen of the NRTIs, NNRTIs and PI; IL-2, IL-12 and pentafuside will be determined by attending clinician in view of the approved doses and dosage regimen in the package insert or as set forth in the protocol taking into consideration the age, sex and condition of the patient and the severity of the HIV-1 infection. See also Tables I-IV hereinafter for dosages and dosage regimens.

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The following clinical protocol may be used to administer the HIV-1 therapy of the present invention:

The study population will include male and female patients diagnosed HIV-1 infection who are either treatment naive or treatment-experienced and will be included if they meet the following inclusion and exclusion criteria:

Subject Inclusion Criteria:

- Subjects diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced.
- HIV-RNA by Amplicor test, Version 1.5 of greater than 500 copies/mL.
- CD₄ + count greater than 100 copies/ml, preferably greater than 200 cells/mL.
- Subjects in good physical health with clinically acceptable safety laboratory test results and ECG.
- The following laboratory parameters must be met:
 - ◆ Platelet count $\geq 100,000/\text{mL}$
 - ◆ Hemoglobin $\geq 9 \text{ gm/dL}$ (90 gm/L)
 - ◆ Absolute neutrophil count $\geq 1500/\mu\text{L}$
 - ◆ Creatinine < 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT $\leq 5 \times$ upper limit of normal
 - ◆ Bilirubin $\leq 2.5 \times$ upper limit of normal
- A negative urine pregnancy test (females only)
- Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.

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Z**Subject Exclusion Criteria**

- Females who are breast-feeding or pregnant or who are not using adequate birth control.
- Subject with allergy to E. coli proteins
- Subjects with a significant past medical/psychiatric history, specifically depression or dementia.

The subjects will be randomized to receive pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b at doses between 0.5 and 4.5 micrograms per kilogram e.g. at doses of 0.5, 1.0, 1.5, 3.0 or 4.5 micrograms per kilogram by subcutaneous injection once a week. HAART may also be initiated before or concurrently with the administration of the pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b

Overall Design and Plan of the Study:

The primary efficacy objective will be lowering of the HIV-I-RNA plasma levels by a factor of 10 or greater.

Plasma HIV-1-RNA/qPCR testing will be performed by a central laboratory. A positive HIV-1-RNA assay result will be required at Baseline; only patients positive for HIV-1-RNA will be eligible to participate.

Table 1

**NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)
DOSAGE & DOSAGE REGIMEN**

<u>NRTI (Tradename, Marketer)</u>	<u>Usual adult dosage</u>
Zidovudine, AZT (Retrovir - Glaxo Wellcome)*	200 mg PO tid or 300 mg PO bid
Stavudine (Zerit - Bristol-Myers Squibb)*	40 mg PO bid ¹
Didanosine (Videx - Bristol-Myers Squibb)*	200 mg PO bid ²
Lamivudine (Epivir - Glaxo Wellcome)*	150 mg PO bid ³
Zalcitabine (Hivid - Roche)	0.75 mg PO tid
Zidovudine plus lamivudine (Combivir - Glaxo Wellcome)	1 tablet PO bid ⁴
Abacavir (Ziagen-Glaxo-Wellcome)	200 or 400 mg PO tid
Adefovir dipivoxil (Prevon-Gilead Sciences)	125 or 200 mg PO qd ⁵
Lobucavir (BMS-180194-BMS)	200 mg PO bid ⁶
BCH-10652 (Biochem Pharma)	200 mg PO, qid 400 mg PO, qid ⁷
Emitricitabine ((-)-FTC-Triangle Pharmaceuticals)	200 mg PO qd ⁸
Beta-L-FD4 (B-L-D4C-Vion Pharmaceutical)	0.2-25 mg/kg/day ⁹
DAPD (Triangle Pharmaceuticals)	_____ ¹⁰
Lodenosine (FddA-U.S. Bioscience)	1.6-3.2 mg/Kg PO bid ¹¹

Footnotes Table 1

- * Available in a liquid formulation.
- ¹ For patients less than 60 kg, 30 mg PO bid.
- ² With tablets; for patients < 60 kg, 125 mg PO bid; >60 kg, 200 mg PO bid;. With powder, dosage varies from 167 mg (< 60 kg) to 250 mg PO (< 60 kg) bid. Doses should be taken at least 30 minutes before meals or at least two hours afterward.
- ³ For patients less than 50 kg, 2 mg/kg PO bid.
- ⁴ Each tablet contains 300 mg of zidovudine and 150 mg of lamivudine.
- ⁵ Available under an expanded access program - a NIH-sponsored Phase III Trial
- ⁶ Phase II

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77Table I Footnotes continued

- 7 Phase I/II; see PharmaProjects, sections J5A & J5Z
- 8 Phase II/III; see PharmaProjects, sections J5A & J5Z
- 9 Preclinical; active in duck HBV model; see PharmaProjects, sections J5A & J5Z
- 10 Preclinical; active po and IV; DAPD is a prodrug of another dioxolene purine, DXG. See PharmaProjects, sections J5A & J5Z
- 11 Phase II, FddA has potential for once-a-day dosage

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Z**TABLE II****NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)
Dosage and Dosage Regimen**

<u>NRTI (Tradename, Marketer)</u>	<u>Usual adult dosage and Dosage Regimen</u>
Nevirapine (Viramune - Roxane)	200 mg PO bid ¹
Delavirdine (Rescriptor - Pharmacia & Upjohn)	400 mg PO tid
Efavirenz (Sustiva, Dupont)	200 mg PO qid ²
PNU-142721 (Pharmacia + Upjohn)	_____ ³
AG-1549 (Agouvon Pharmaceuticals)	_____ ⁴
MKC-442 (Triangle Pharmaceuticals)	750 mg PO bid ⁵
(+)-Calanolide A (Med Chem Research)	800 mg PO ⁶

- ¹ For the first two weeks of treatment with nevirapine, to decrease the risk of rash, patients should take only one 200-mg tablet per day.
- ² Quadruple Therapy of efavirenz with indinavir + 2 NRTIs or Triple Therapy of efavirenz + AZT + lamivudine.
- ³ Preclinical Phase; see PharmaProjects, sections J5A & J5Z
- ⁴ Phase I/II evaluating dose and concomitant use with other anti-HIV-1 therapies; see PharmaProjects, sections J5A & J5Z.
- ⁵ Triple Therapy of (a) MKC-442 with stavudine and either lamivudine or didanosine or (b) MKC-442 with nelfinavir (qv) and NRTIs.
- ⁶ Phase I; see PharmaProjects, sections J5A & J5Z

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Z**TABLE III****Protease Inhibitor (PI) Dosage and Dosage Regimen**

<u>PI (Tradename, Marketer)</u>	<u>Dosage + Dosage Regimen</u>
Saquinavir (Invirase - hard gel capsule- Roche) (Fortovase - soft gel capsule -Roche)	600 mg PO tid ¹ 1100 mg PO tid ¹
Ritonavir (Norvir - Abbott)	600 mg PO bid ²
Indinavir (Crixivan - Merck)	800 mg PO qid ³
Nelfinavir (Viracept - Agouron)	750 mg PO tid ⁴
Amprenavir (141W94, Glaxo)	900 mg - 1200 mg PO bid ⁵
Lasinavir (BMS-234475, BMS)	_____ ⁶
DMP-450 (Triangle Pharmaceuticals)	_____ ⁷
BMS-2322623 (BMS)	_____ ⁸
ABT-378 (Abbott)	60 mg PO bid ⁹
Yisum Project No. 11607 (Yisum)	_____ ¹⁰

¹ With, or within two hours after, a full meal.² With food. The liquid formulation has an unpleasant taste; the manufacturer suggests taking it with chocolate milk or a liquid nutritional supplement.³ With water, one hour before or two hours after a meal. Patients taking indinavir should drink at least 48 ounces (1.5 liter) of water daily.⁴ With food.⁵ Quadruple Combination Therapy of amprenavir with AZT + lamivudine + abacavir.⁶ Phase I/II; see Pharmaprojects, sections J5A & J5Z.⁷ Phase II; see Pharmaprojects, sections J5A & J5Z.⁸ Preclinical Studies; Prodrug esters of BMS 2322623 enhance oral absorption; see Pharmaprojects, sections J5A & J5Z.⁹ Phase I Studies show ABT-378 to be 10X more potent than ritonavir; see Pharmaprojects sections J5A & J5Z.¹⁰ Preclinical; see Pharmaprojects, sections J5A & J5Z.

Other Anti-HIV-1 Drugs

1 Triple Therapy of hydroxyurea with 400 mg ddl + 500 mg AZT ; see PharmaProjects,section
B3C1

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We claim:

1. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower detectable HIV-1-RNA.
- 2 The method of claim 1, wherein the patients are treatment-naive patients.
3. The method of claim 1, wherein the patients are treatment-experienced patients.
- 4 The method of claim 1, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.
5. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.
6. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram QW.
- 7 . The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.

8. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b.
9. The method of claim 1 wherein the pegylated interferon alfa-2b is administered in association with an anti-HIV-1 drug therapy.
10. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the pegylated interferon alfa-2b is administered in association with HAART.
11. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.
12. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms QW.
13. A method of treating patients having HIV-1 infections which comprises administering about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week.
14. The method of claim 13, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.
15. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically

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effective amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

16. The method of claim 15 wherein the anti-HIV-1 drug therapy is HAART.

17. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

18. The method of claim 17 wherein the anti-HIV-1 drug therapy is HAART.

19. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered QW for at least about 2 to 4 weeks prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

20. The method of claim 19 wherein the anti-HIV-1 drug therapy is HAART.

21. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered after administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

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22. The method of claim 21, wherein the anti-HIV-1 drug therapy is HAART.

23. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa.

24. The method of claim 23, wherein the an anti-HIV-1 drug therapy is HAART.

25. The method of claim 23, wherein the patients are treatment-naive patients.

26. The method of claim 23, wherein the patients are treatment-experienced patients.

27. The method of claim 23, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.

28. The method of claim 23, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.

29. The method of claim 23, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram QW.

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30. The method of claim 23, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.

31. The method of claim 23, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.

32. The method of claim 23, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms QW.

33. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

34. The method of claim 33, wherein the an anti HIV-1 drug therapy is HAART.

35. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

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36. The method of claim 35, wherein the an anti HIV-1 drug therapy is HAART.

37. The method of claim 35, wherein the pegylated interferon-alfa-2b is administered QW for at least about 2 to 4 weeks prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

38. The method of claim 35, wherein the an anti HIV-1 drug therapy is HAART.

39. The method of claim 35, wherein the pegylated interferon-alfa-2b is administered after administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

40. The method of claim 39, wherein the an anti HIV-1 drug therapy is HAART.

41. A method of treating patients having HIV-1 infections which comprises (1) administering in a first treatment time period of at least about two to about four weeks about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week , followed by (2) administering in a second treatment time period, a therapeutically effective amount of an anti HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa-2b once a week.

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42. The method of claim 41, wherein the an anti HIV-1 drug therapy is HAART.

43. The method of claim 41, wherein about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

44. The method of claim 41, wherein about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

45. The method of claim 41, wherein about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

46. The method of claim 41, wherein the patients are treatment-naive patients.

47. The method of claim 41, wherein the patients are treatment-experienced patients.

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DECLARATION AND POWER OF
ATTORNEY FOR PATENT APPLICATION

Attorney's Docket No. IN01003 K

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

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

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

HIV THERAPY

the specification of which

☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____

and was amended on _____ (if applicable).

☐ was filed on _____ as PCT International Application No. _____

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

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Priority Claimed

_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	_____ Yes or No
-------------------	--------------------	---------------------------------	--------------------

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

ATTORNEY
DOCKET # IN01003
(Application Number)

March 2, 1999
(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)

(Filing Date)

(Status - patented, pending, abandoned)

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7/

Power of Attorney: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in Patent and Trademark Office connected therewith. (List name and registration number.)

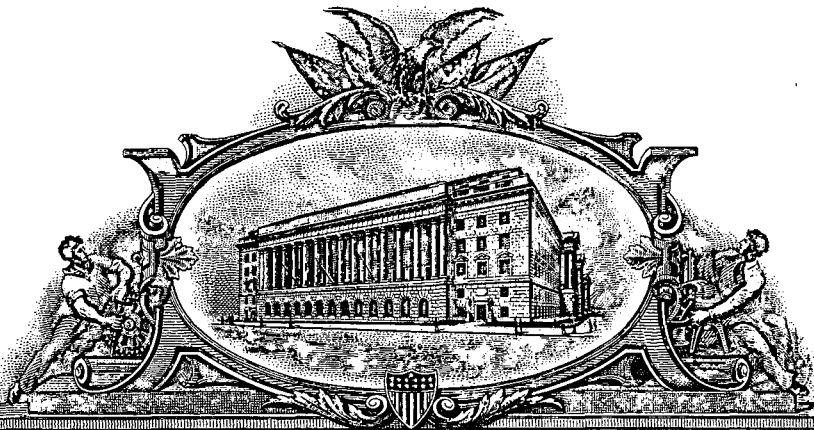
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--	---

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APPLICATION NUMBER: 09/288,358

FILING DATE: April 08, 1999



By Authority of the

COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN

Certifying Officer

1c645 U.S. PTO
04/08/99

PATENT

Attorney Docket No.: IN01003K1

Box Patent Application
ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application, including a specification and claim(s), of:

Inventors: Mark A. Laughlin, Paul W. Glue and Carlos O. Stalgis

Title: HIV THERAPY

Also enclosed are items 1-6, as checked:

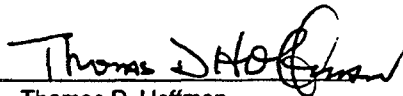
1. ☐ _____ sheets of drawing(s).
2. ☒ Declaration and Power of Attorney (3 pages, unexecuted).
 - a. ☐ Newly executed.
 - b. ☐ Copy from a prior application (box no. 10 below also completed).
 - (i). ☐ A signed statement is enclosed deleting inventor(s) named in the prior application.
 - (ii). ☐ The entire disclosure of the prior application, from which a copy of the declaration is supplied, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
3. ☐ A floppy disk, including the computer form of the Sequence Listing in the specification. The undersigned certifies that the computer form is equivalent in content to the Sequence Listing in the specification.
4. ☐ A preliminary amendment.
5. ☐ An information Disclosure Statement (PTO Form 1449) with copies of _____ cited documents.
6. ☐ _____
7. ☒ The filing fee is as follows, calculated after entry of any preliminary amendment:

For	Number Filed (1)	Number Extra (2)	Rate	Fee
Basic Fee				\$760.00
Total Claims	64- 20 =44	(44)	x \$18.00	\$792.00
Independent Claims	5- 3 =2	(2)	x \$78.00	\$156.00
Multiple Dependent Claims				\$0.00
			TOTAL FILING FEE	\$1708.00

*If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

JC625 U.S. PTO
09/288358
04/08/99

- 75
8. ☒ The Commissioner is authorized to charge Deposit Account No. 19-0365 in the amount of the above Total Filing Fee. A duplicate of this form is enclosed for fee processing.
9. ☒ General Authorization. This paper constitutes a general authorization to the Commissioner, for any deficiency in the above Total Filing Fee and all fee requirements subsequent to the instant filing, to charge all fees for amendments, petitions, and any and all other papers to our Deposit Account 19-0365. This is not, however, an automatic authorization to charge our Deposit Account for the Issue Fee.
10. ☒ This application is a request for filing a ☐ Continuation ☐ Divisional ☒ Continuation -in-part of prior application Serial No. 09/268,521, filed on March 12, 1999, which is a Continuation - in-part of prior application Serial No. 09/260,388, filed on March 2, 1999



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Date of Deposit: April 8, 1999

Rev. 3/99 ss

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PATENT CASE
IN01003K1

HIV THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS: This application is a continuation-in-part of commonly-owned U.S. Patent Application SN 09/268,521, filed on March 12, 1999, which is a continuation-in-part of commonly-owned U.S. Patent Application SN 09/260,388, filed on March 2, 1999.

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating patients having immunodeficiency virus type-1 ("HIV-1") infections by administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-1-RNA .

A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART") ; HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naïve patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

The present invention provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-RNA.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 therapy in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering, in a second treatment time period, a therapeutically effective amount of an anti-HIV-1 therapy in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering, in a second treatment time period, a

therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

The present invention also provides a method of treating pediatric patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with pegylated interferon-alfa.

DETAILED DESCRIPTION

The present method of treating patients having HIV-1 infections comprises administering a therapeutically effective amount of pegylated interferon-alfa as monotherapy or in association with a therapeutically effective amount of at least one of ribavirin, interleukin-2("IL-2"), interleukin-12(" IL-12"), and pentafuside alone or in combination with an anti-HIV-1 therapy, especially, HAART in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. See for example A-M. Vandamme et al., in Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) and "Drugs for HIV Infection" in The Medical Letter Vol. 39 (Issue 1015) December 5, 1997, pages 111-116.. The initiation of the HAART may occur before, after or concurrently with administering a therapeutically effective amount of pegylated interferon-alfa in accordance with the present invention. In an embodiment of the present invention, the method of treating patients having HIV-1 infections comprises two treatment time periods. In the first treatment time period, a therapeutically effective amount of pegylated interferon-alfa is administered for a first treatment time period sufficient to lower HIV-1-RNA plasma levels, preferably by a power of 10, more preferably by at least two powers of ten, i.e., at least 10^2 , lower than the initial HIV-1-RNA plasma level. In the second treatment time period, the method entails

continuing the administration of a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of HAART in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections, including when to start multidrug therapy and which drugs to combine. The triple drug therapy may include two NRTIs and one PI, but there are many issues to be considered in the choice of the precise HAART for any patient. See for example, Tables 1 & 2 and Figure 2 in A-M. Vandamme et al., listed hereinabove.

The term "patients having HIV-1 infections" as used herein means any patient -including a pediatric patient-having HIV-1 infection and includes treatment-naive patients and treatment-experienced patients having the HIV-1 infection as well as treatment-naive patients and treatment-experienced patients co-infected with the HIV-1 and hepatitis C virus ("HCV").

The term "pediatric patient" as used herein means a patient below the age of 17, and normally includes those from birth to 16 years of age.

The term "treatment-naive patients" as used herein means patients having HIV-1 or co-infected with the HIV-1 and HCV who have never been treated with any anti-retroviral drugs, e.g., NRTI, NNRTI, PI or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

The term "treatment-experienced" patients as used herein means those patients having HIV-1 or co-infected with the HIV-1 and HCV who have initiated some form of anti HIV therapy including, but not limited to

HAART or some form of anti-HCV therapy, including but not limited to interferon-alfa, pegylated interferon alfa or ribavirin.

The term "patients having hepatitis C infections" as used herein means any patient-including a pediatric patient- having hepatitis C and includes treatment-naive patients having hepatitis C infections and treatment-experienced patients having hepatitis C infections as well as those pediatric, treatment-naive and treatment-experienced patients having chronic hepatitis C infections.

These patients having hepatitis C include those who are infected with multiple HCV genotypes including type 1 as well as those infected with, e.g., HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.

The term "treatment-naive patients having hepatitis C infections" as used herein means patients with hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

The term "treatment-experienced patients having hepatitis C infections" as used herein means patients with hepatitis C who have been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa, including relapsers and non-responder.

The term "relapsers" as used herein means treatment-experienced patients with hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

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The term "non-responders" as used herein means treatment-experienced patients with hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), preferably in the range of about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW), or is in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.25 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, or is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, most preferably is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 0.75 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week.

When the pegylated interferon-alfa administered to pediatric patients is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment

in accordance with the present invention, including in first and second treatment time periods is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), or about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week, or preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, and most preferably about 2.25 to about 2.6 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 1.1 to about 1.3 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW).

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 200 micrograms to about 250 micrograms QW or the effective amount is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 100 micrograms to about 125 micrograms twice a week.

When the pegylated interferon-alfa administered to a pediatric patient is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered during the treatment in accordance with the present invention, including in first treatment time period is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 300 micrograms to about 375 micrograms QW or the therapeutically effective amount of pegylated interferon alfa-2a administered to a pediatric patient is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 150 micrograms to about 190 micrograms once a week

Ribavirin is administered to the patient in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of ribavirin. The amount of ribavirin administered concurrently with the pegylated interferon-alfa is from about 400 to about 1600 mg per day, preferably about 600 to about 1200 mg/day or about 800 to about 1200 mg day and most preferably about 1000 to about 1200 mg/kg a day. The pegylated interferon-alfa dose is also preferably administered to the pediatric patient during the same period of time that such patient receives doses of ribavirin. The amount of ribavirin administered to the pediatric patient concurrently with the pegylated interferon-alfa is from about 8 to about 15 mg per kilogram per day, preferably about 8, 12 or 15 mg per kilogram per day, in divided doses.

Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Ribavirin may be administered orally in capsule, tablet or

liquid form in association with the parenteral administration of pegylated interferon-alfa . Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NTRI" s) as used herein means nucleosides and nucleotides and analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HIVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN tradename from Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON tradename from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Laval, Quebec

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H7V, 4A7, Canada; emitricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4(also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluorocytidine) licensed by Yale University to Vion Pharmaceuticals, New Haven CT 06511; and DAPD, the purine nucleoside, (-)-beta-D-2,6,-diaminopurine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and Iodenosine (FddA), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, a acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohocken, PA. 19428.

The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

Typical suitable non-nucleoside reverse transcriptase inhibitors include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delaviradine (BHAP, U-90152) available under the RESCRIPTOR tradename from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename from DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, a furopyridine-thiopyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5- (3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 1-(ethoxymethyl)-5-(1-methylethyl)-6-

(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN (available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

Typical suitable protease inhibitors include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOUASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfnavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla, CA 92037-1020; amprenavir (141W94), a non-peptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont

and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543 as a 2nd-generation HIV-1 PI; and ABT-378 under development by Abbott, Abbott Park, IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020;

The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the triple and quadruple combination therapies called HAART.

Typical suitable anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from , NNRTIs and PIs ;see Talbes I, II and III, hereinafter.

Typical suitable HAART - multidrug combination therapies- include (a) triple combination therapies such as two NRTIs and one PI ; or (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment-naive patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is preferred unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺ and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug, e.g., one PI or one NNRTI could be added. See the Table A hereinbelow.

Table A

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES

A. Triple Combination Therapies

1. Two NRTIs¹ + one PI²
2. Two NRTIs¹ + one NNRTI³

B. Quadruple Combination Therapies⁴

Two NRTIs + one PI + a second PI or one NNRTI

C. ALTERNATIVES:⁵

Two NTRI¹

One NTRI⁵ + one PI²

Two PIs⁶ ± one NTRI⁷ or NNRTI³

One PI² + one NRTI⁷ + one NNRTI³

FOOTNOTES TO TABLE A

1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine; See also Table I
2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules. Ritonavir is used less frequently because of troublesome adverse effects. The old formulation of saquinavir was used least often because of its poor bioavailability and limited effectiveness, but the new saquinavir formulation should be more effective. See also Table III.
3. Nevirapine or delavirdine. See also Table II
4. See A-M. Vandamme et al Antiviral Chemistry + Chemotherapy 9:187 at p 193-197 and Figures 1 + 2.

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5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV-resistance and clinical failure in many patients.
6. Most data obtained with saquinavir and zidovudine (each 400 mg bid). See also Table III
7. Zidovudine, stavudine or didanosine. See also Table I

Other anti-HIV-1 drugs useful for administration in association with pegylated interferon alfa include hydroxyurea, ribavirin, IL-2 and IL-12, and Yisum Project No. 11607. These above-listed anti-HIV-1 drugs may also be administered in association with pegylated interferon alfa in association with any anti-HIV-1 drug therapy, especially the triple and quadruple drug combinations called HAART.

Hydroxyurea (Droxia) is a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells. Hydroxyurea discovered at the NCI is under development by Bristol-Myers Squibb. In preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine.

Yisum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein under preclinical development by Yisum Research Development Co., Jerusalem 91042, Israel.

The pegylated interferon alfa, PEG₁₂₀₀₀-IFN-alfa2b (available from Schering-Plough Research Institute, Kenilworth, NJ) increased the in vitro anti HIV-1 activity of ribavirin. The combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited HIV replication in vitro using phytohemagglutinin ("PHA" - P) - activated peripheral blood mononuclear

cells ("PBMCs") at doses corresponding to plasmatic concentrations observed in animals and man. Healthy PBMCs were separated from a buffy-coat of one HIV-seronegative blood donor by Ficoll-Hypaque density gradient centrifugation. PBMCs were activated by 1 µg/ml phytohemagglutinin (PHA-P) for two days in cell culture medium A: RPMI 1640 supplemented with 10% heat-inactivated (+56°C, 45 min.) fetal calf plasma (FCS), 2 mM L-glutamine and a tri-antibiotic mixture (penicillin, streptomycin, neomycin; PSN). After these two days, cells were washed and cultured at one million cell per milliliter in cell culture medium B: cell culture medium A supplemented with 20 IU/ml recombinant human interleukin-2. Cells were maintained at +37°C in a 5% CO₂-air humidified atmosphere. Experiments were repeated twice with cells of other blood donors. In total, three independent experiments were performed.

PBMCs were infected with 1,000 50% Tissue Culture Infectious Doses (TCID₅₀) of the reference HIV-1-LAI strain [F.Barre'-Sinoussi, Science, 1983, 220, 868-871]. This strain has been amplified using PHA-P-activated umbilical blood mononuclear cells (UBMC). Viral stock has been then titrated on PHA-P activated PBMC by end-point dilution. TCID₅₀ was then calculated using Karber's formula [Arch. Exp. Path. Pharmacol., 1931, 162, 126-133].

PEG₁₂₀₀₀-IFN-α2b and ribavirin, alone and in combination, and AZT used as a control, were administrated 24 hours before HIV-1 infection and maintained all along the culture. Three doses of PEG₁₂₀₀₀-IFN-α2b and ribavirin were used.

200,000 PHA-P-activated PBMCs were added to each well of 96-well microplates. Cells were 24 hour-pretreated prior to infection with the

reference HIV-1-LAI strain. Twice a week, cell supernatants were collected, and drugs and medium were renewed. At day 7, RT activity were determined in cell supernatants, and potential cytotoxic effects of drugs and drug combinations were evaluated by microscopic observation.

Viral replication was measured by determining reverse transcriptase ("RT") activity in cell supernatants using Retro-Sys® kit, according to manufacturer's recommendations (Innovagen, Lund, Sweden).

Effective doses were calculated using cumulative RT activities with Chou J. and TC. microcomputer software.

The combined effects were analyzed using either the combination index (CI) [Chou & Talalay, 1984] with J and TC Chou microcomputer software, or the fractionary inhibitory concentration (FIC) index [Antimicrob. Agents. Chemother., 1987, 31, 1613-1617]. When the CI or FIC index is equal to 1, the combination is additive. When it is below 1.0, the combination is synergistic, and when it is above 1.0, the combination is judged as antagonistic.

PEG₁₂₀₀₀-IFN- α 2b as well as the combination of PEG₁₂₀₀₀-IFN- α 2b and ribavirin inhibited the HIV replication at doses corresponding to plasmatic concentrations measured in mice and HIV-1 infected patients [BE. Gilbert, et al. Antimicrob. Agents Chemother., 1988, 32, 117-121; E. Connor et al., Antimicrob. Agents Chemother., 1993, 37, 537-539].

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IL-2 is disclosed in Ajinomoto EP-0142268 , Takeda EP-0176299, and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314 is available under the PROLEUKIN(aldesleukin) tradename from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration upon reconstitution and dilution with water; doses of about 1 to about 20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred.

IL-12 is disclosed in WO96/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 microgram/kg/day, sc.

Pentafuside (DP-178, T-20) a 36-amino acid synthetic peptide, disclosed in U.S. Patent No. 5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc infusion or injection together with efavirenz and 2 PI's to HIV-1 positive patients refractory to a triple combination therapy; use of 100 mg/day is preferred.

The term " interferon-alfa " as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon

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available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG₁₂₀₀₀-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG₁₂₀₀₀-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG₁₂₀₀₀-interferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG₁₂₀₀₀ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG₁₂₀₀₀ attached.

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The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human plasma albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosal, cresol or benylalcohol), and surfactants(e.g. tween or polysorbates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos,

4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

- (a) elevated ALT,
- (b) positive test for anti-HCV antibodies,
- (c) presence of HCV as demonstrated by a positive test for the presence of HCV-RNA in the serum,
- (d) clinical stigmata of chronic liver disease,
- (e) hepatocellular damage.

To practice the invention, the combination therapy of pegylated interferon-alfa and ribavirin is administered in association with anti-retroviral therapy, e.g., HAART, to the patient having HIV-1 infection and exhibiting one or more of the above signs or symptoms in the first and second treatment time periods in amounts sufficient to eliminate or at

least alleviate one or more of the signs or symptoms., and to lower the HCV-RNA serum levels by at least a power of ten, and preferably to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period. The sum of the first and second treatment time periods is about 40-50 weeks, and preferably is 48 weeks. Administration of the ribavirin may be discontinued after the end of the second time period depending upon the judgment of the attending clinician.

The term "no detectable HCV-RNA" in the context of the present invention means that there are fewer than 100 copies of HCV-RNA per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is 100 copies/mL. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

In a preferred embodiment of the present invention, those patients co-infected with HIV-1 and HCV infections are treated with pegylated interferon alfa in combination with ribavirin and a HAART combination considered appropriate by the attending clinician and the patient; use of the interferon alfa-2b-ribavirin combination therapy sold by Schering Corp. under the REBETRON tradename is preferred. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499). Ribavirin, 1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck

Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

For the pediatric patient co-infected with the HIV-1 and HCV infections, a suitable HAART includes a NRTI+ a PI, e.g., Nelfinavir +a NNRTI, e.g., Efavirenz in combination with the dosages and dosage regimens for pegylated interferon alfa and ribavirin listed herein above. See also Tables I-IV herein below. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may be administered to these pediatric patients in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician to reduce retardation of growth associated with pegylated interferon alfa treatment.

HAART is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose may be administered before, after or during the same period of time that the patient receives doses of HAART. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may also be administered -in association with HAART and pegylated interferon alfa- to the pediatric patient having HIV-1 infection in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician.

In a preferred embodiment of the present invention, pegylated interferon alfa is administered to HIV-1 infected patients prior to initiation of HAART, and preferably about two to about four weeks prior to initiation of HAART. In another preferred embodiment of the present invention, administration of pegylated interferon alfa is initiated concurrently, i.e.,

on the same day with the administration of HAART. In another preferred embodiment of the present invention the pegylated interferon-alfa is administered after the HIV-1 infected patient has initiated HAART.

The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnostics) or of Nuclisens HIV-1 QT -1. This methodology is described by Schooley, RT, Antiviral Therapy(1997), 2 (Suppl. 4):59-70 .

The doses and dosage regimen of the NRTIs, NNRTIs and PI; IL-2, IL-12 and pentafuside will be determined by attending clinician in view of the approved doses and dosage regimen in the package insert or as set forth in the protocol taking into consideration the age, sex and condition of the patient and the severity of the HIV-1 infection. For the pediatric patient infected with the HIV-1, or co-infected with the HIV-1 and HCV infections a suitable HAART includes a NRTI+ a PI, e.g., Nelfinavir +a NNRTI, e.g., Efavirenz in combination with the dosages and dosage regimens for pegylated interferon alfa and ribavirin listed herein above. See also Tables I-IV hereinafter for dosages and dosage regimens.

The following clinical protocol may be used to administer the HIV-1 in accordance with the therapy of the present invention. Many modifications of this clinical protocol will be obvious to the skilled

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clinician, and the following Study Design should not be interpreted as limiting the scope of the method of this invention which is only limited by the claims listed hereinafter. See for example J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

The study population will include male and female patients diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced and will be included if they meet the following inclusion and exclusion criteria:

Subject Inclusion Criteria:

- Subjects diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced.
- HIV-RNA by Amplicor test, Version 1.5 of greater than 500 copies/mL.
- CD₄ + count greater than 100 copies/ml, preferably greater than 200 cells/mL.
- Subjects in good physical health with clinically acceptable safety laboratory test results and ECG.
- The following laboratory parameters must be met:
 - ◆ Platelet count $\geq 100,00/mL$
 - ◆ Hemoglobin ≥ 9 gm/dL (90 gm/L)
 - ◆ Absolute neutrophil count $\geq 1500/\mu L$
 - ◆ Creatinine < 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT ≤ 5 x upper limit of normal

- ◆ Bilirubin ≤ 2.5 x upper limit of normal
- A negative urine pregnancy test (females only)

Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.

Subject Exclusion Criteria

- Females who are breast-feeding or pregnant or who are not using adequate birth control.
- Subject with allergy to E. coli proteins
- Subjects with a significant past medical/psychiatric history, specifically depression or dementia.

The subjects will be randomized to receive pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b at doses between 0.5 and 4.5 micrograms per kilogram e.g. at doses of 0.5, 1.0, 1.5, 3.0 or 4.5 micrograms per kilogram by subcutaneous injection once a week. HAART may also be initiated before or concurrently with the administration of the pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b

Overall Design and Plan of the Study:

The primary efficacy objective will be lowering of the HIV-1-RNA plasma levels by a factor of 10 or greater.

Plasma HIV-1-RNA/qPCR testing will be performed by a central laboratory. A positive HIV-1-RNA assay result will be required at Baseline; only patients positive for HIV-1-RNA will be eligible to participate.

Table 1

**NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)
DOSAGE & DOSAGE REGIMEN**

<u>NRTI (Tradename, Marketer)</u>	<u>Usual adult dosage</u>
Zidovudine, AZT (Retrovir - Glaxo Wellcome)*	200 mg PO tid or 300 mg PO bid
Stavudine (Zerit - Bristol-Myers Squibb)*	40 mg PO bid ¹
Didanosine (Videx - Bristol-Myers Squibb)*	200 mg PO bid ²
Lamivudine (Epivir - Glaxo Wellcome)*	150 mg PO bid ³
Zalcitabine (Hivid - Roche)	0.75 mg PO tid
Zidovudine plus lamivudine (Combivir - Glaxo Wellcome)	1 tablet PO bid ⁴
Abacavir (Ziagen-Glaxo-Wellcome)	200 or 400 mg PO tid
Adefovir dipivoxil (Prevon-Gilead Sciences)	125 or 200 mg PO qd ⁵
Lobucavir (BMS-180194-BMS)	200 mg PO bid ⁶
BCH-10652 (Biochem Pharma)	200 mg PO, qid 400 mg PO, qid ⁷
Emitricitabine ((-)-FTC-Triangle Pharmaceuticals)	200 mg PO qd ⁸
Beta-L-FD4 (B-L-D4C-Vion Pharmaceutical)	0.2-25 mg/kg/day ⁹
DAPD (Triangle Pharmaceuticals)	10
Lodenosine (FddA-U.S. Bioscience)	1.6-3.2 mg/Kg PO bid ¹¹

Footnotes Table 1

- * Available in a liquid formulation.
- ¹ For patients less than 60 kg, 30 mg PO bid.
- ² With tablets; for patients < 60 kg, 125 mg PO bid; >60 kg, 200 mg PO bid;. With powder, dosage varies from 167 mg (< 60 kg) to 250 mg PO (< 60 kg) bid. Doses should be taken at least 30 minutes before meals or at least two hours afterward.
- ³ For patients less than 50 kg, 2 mg/kg PO bid.
- ⁴ Each tablet contains 300 mg of zidovudine and 150 mg of lamivudine.
- ⁵ Available under an expanded access program - a NIH-sponsored Phase III Trial
- ⁶ Phase II

Table 1 Footnotes continued

- 7 Phase I/II; see PharmaProjects, sections J5A & J5Z
- 8 Phase II/III; see PharmaProjects, sections J5A & J5Z
- 9 Preclinical; active in duck HBV model; see PharmaProjects, sections J5A & J5Z
- 10 Preclinical; active po and IV; DAPD is a prodrug of another dioxolene purine, DXG. See PharmaProjects, sections J5A & J5Z
- 11 Phase II, FddA has potential for once-a-day dosage

TABLE II

**NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)
Dosage and Dosage Regimen**

<u>NRTI (Tradename, Marketer)</u>	<u>Usual adult dosage and Dosage Regimen</u>
Nevirapine (Viramune - Roxane)	200 mg PO bid ¹
Delavirdine (Rescriptor - Pharmacia & Upjohn)	400 mg PO tid
Efavirenz (Sustiva, Dupont)	200 mg PO qid ²
PNU-142721 (Pharmacia + Upjohn)	_____ ³
AG-1549 (Agouvon Pharmaceuticals)	_____ ⁴
MKC-442 (Triangle Pharmaceuticals)	750 mg PO bid ⁵
(+)-Calanolide A (Med Chem Research)	800 mg PO ⁶

- ¹ For the first two weeks of treatment with nevirapine, to decrease the risk of rash, patients should take only one 200-mg tablet per day.
- ² Quadruple Therapy of efavirenz with indinavir + 2 NRTIs or Triple Therapy of efavirenz + AZT + lamivudine.
- ³ Preclinical Phase; see PharmaProjects, sections J5A & J5Z
- ⁴ Phase I/II evaluating dose and concomitant use with other anti-HIV-1 therapies; see Pharmaprojects, sections J5A & J5Z.
- ⁵ Triple Therapy of (a) MKC-442 with stavudine and either lamivudine or didanosine or (b) MKC-442 with nelfinavir (qv) and NRTIs.
- ⁶ Phase I; see Pharmaprojects, sections J5A & J5Z

TABLE III**Protease Inhibitor (PI) Dosage and Dosage Regimen**

<u>PI (Tradename, Marketer)</u>	<u>Dosage + Dosage Regimen</u>
Saquinavir (Invirase - hard gel capsule- Roche) (Fortovase - soft gel capsule -Roche)	600 mg PO tid ¹ 1100 mg PO tid ¹
Ritonavir (Norvir - Abbott)	600 mg PO bid ²
Indinavir (Crixivan - Merck)	800 mg PO qid ³
Nelfinavir (Viracept - Agouron)	750 mg PO tid ⁴
Amprenavir (141W94, Glaxo)	900 mg - 1200 mg PO bid ⁵
Lasinavir (BMS-234475, BMS)	_____ ⁶
DMP-450 (Triangle Pharmaceuticals)	_____ ⁷
BMS-2322623 (BMS)	_____ ⁸
ABT-378 (Abbott)	60 mg PO bid ⁹

¹ With, or within two hours after, a full meal.

² With food. The liquid formulation has an unpleasant taste; the manufacturer suggests taking it with chocolate milk or a liquid nutritional supplement.

³ With water, one hour before or two hours after a meal. Patients taking indinavir should drink at least 48 ounces (1.5 liter) of water daily.

⁴ With food.

⁵ Quadruple Combination Therapy of amprenavir with AZT + lamivudine + abacavir.

⁶ Phase I/II; see Pharmaprojects, sections J5A & J5Z.

⁷ Phase II; see Pharmaprojects, sections J5A & J5Z.

⁸ Preclinical Studies; Prodrug esters of BMS 2322623 enhance oral absorption; see Pharmaprojects, sections J5A & J5Z.

⁹ Phase I Studies show ABT-378 to be 10X more potent than ritonavir; see Pharmaprojects sections J5A & J5Z.

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7/2**TABLE IV**

Other Anti-HIV-1 Drugs

<u>Drug (Trade Name, Marketer)</u>	<u>Usual Adult Dosage and Dosage Regimen</u>
Hydroxyurea (Droxia, BMS)	1000 mg PO qid ¹
Ribavirin(Rebetol, Schering-Plough)	600mg-1200mg/day, PO
IL-2(Proleukin, Chiron Corp.)	1 -20million IU/day, sc
IL-12(Roche)	0.5-10 micrograms/kg/day, sc
Yisum Project No. 11607 (Yisum)	_____ ²

¹ Triple Therapy of hydroxyurea with 400 mg ddl + 500 mg AZT ; see PharmaProjects, section B3C1

² Preclinical; see Pharmaprojects, sections J5A & J5Z.

We claim:

1. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower detectable HIV-1-RNA.
2. The method of claim 1, wherein the patients are treatment-naive patients.
3. The method of claim 1, wherein the patients are treatment-experienced patients.
4. The method of claim 1, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.
5. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram per week.
6. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram per week.
7. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram per week.

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8. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b.
9. The method of claim 1 wherein the pegylated interferon alfa-2b is administered in association with an anti-HIV-1 drug therapy.
10. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the pegylated interferon alfa-2b is administered in association with HAART.
11. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms per week.
12. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms per week.
13. A method of treating patients having HIV-1 infections which comprises administering about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.
14. . The method of claim 13, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.
15. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically

effective amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

16. The method of claim 15 wherein the anti-HIV-1 drug therapy is HAART.

17. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

18. The method of claim 17 wherein the anti-HIV-1 drug therapy is HAART.

19. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered QW for at least about 2 to 4 weeks prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

20. The method of claim 19 wherein the anti-HIV-1 drug therapy is HAART.

21. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered after administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

22. The method of claim 21, wherein the anti-HIV-1 drug therapy is HAART.
23. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa 2b per week.
24. The method of claim 23, wherein the an anti-HIV-1 drug therapy is HAART.
25. The method of claim 23, wherein the patients are treatment-naïve patients.
26. The method of claim 23, wherein the patients are treatment-experienced patients.
27. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram in a single dose QW or divided doses BIW
28. . The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram in a single dose QW or divided doses BIW
29. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

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Figure 1

38. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.375 to about 1.5 micrograms per kilogram BIW.

39. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered to a patient co-infected with HCV in association with administering a therapeutically effective amount of ribavirin, in combination with a therapeutically effective amount of HAART.

40. A method of treating patients having HIV-1 infections which comprises (1) administering in a first treatment time period of at least about two to about four weeks about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering in a second treatment time period, a therapeutically effective amount of an anti HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa-2b per week.

41. The method of claim 40, wherein the an anti HIV-1 drug therapy is HAART.

42. The method of claim 40, wherein about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

43. The method of claim 40, wherein about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

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44. The method of claim 40, wherein about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.
45. The method of claim 40, wherein the patients are treatment-naive patients.
46. The method of claim 40, wherein the patients are treatment-experienced patients.
47. A method of treating pediatric patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with pegylated interferon-alfa.
48. The method of claim 47, wherein the an anti-HIV-1 drug therapy is HAART.
49. The method of claim 47, wherein the pediatric patients are treatment-naive patients.
50. The method of claim 47, wherein the pediatric patients are treatment- experienced patients.
52. The method of claim 47, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.
53. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of

pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.

54. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 4.5 micrograms per kilogram QW.

55. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 2.25 to about 2.6 micrograms per kilogram QW.

56. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.

57. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 300 to about 375 micrograms QW.

58. The method of claim 47, wherein the pediatric patient is co-infected with HCV.

59. The method of claim 58, wherein ribavirin is administered to the pediatric patient in association the pegylated interferon-alfa and the amount of ribavirin is in a range of about 8 to about 15 mg per kilogram per day, in divided doses..

60. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram BIW

61. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.25 to about 2.25 micrograms per kilogram BIW.

62. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 1.1 to about 21.3 micrograms per kilogram BIW.

63. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms BIW.

64. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 150 to about 190 micrograms BIW.

ABSTRACT OF THE DISCLOSURE

Methods for treating treatment-naïve as well as treatment-experienced adult and pediatric patients having HIV-1 infections as well as patients co-infected with HIV-1 and HCV involving administering a therapeutically effective amount of pegylated interferon-alfa, e.g., pegylated interferon alfa-2b as monotherapy or preferably in association with a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy, e.g., HAART are disclosed.

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**DECLARATION AND POWER OF
ATTORNEY FOR PATENT APPLICATION**

Attorney's Docket No. IN01003K1

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

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

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

☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____
and was amended on _____ (if applicable).

☐ was filed on _____ as PCT International Application No. _____

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

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):	Priority Claimed		
(Number)	(Country)	(Day/Month/Year Filed)	Yes or No

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

(Application Number)	(Filing Date)
----------------------	---------------

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

09/260,388	March 2, 1999	PENDING
(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)
09/268,521	March 12, 1999	PENDING
(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)

Power of Attorney: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in Patent and Trademark Office connected therewith. (List name and registration number.)

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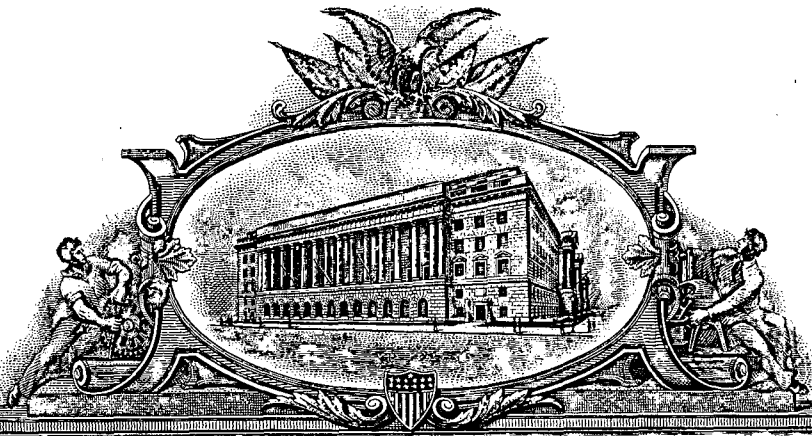
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Rev. 2/96 JHB

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February 04, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/454,004

FILING DATE: December 03, 1999



**By Authority of the
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**P. SWAIN
Certifying Officer**

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UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))	Attorney Docket No.	IN01003K2
	First Inventor or Application Identifier	Laughlin, et al
	Title	HIV THERAPY
	Express Mail Label No.	EL226886702US

APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.		ADDRESS TO: Assistant Commissioner for Patents Box Patent Application Washington, DC 20231			
1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)	5. ☐ Microfiche Computer Program (Appendix)	ACCOMPANYING APPLICATION PARTS 7. ☐ Assignment Papers (cover sheet & document(s)) 8. ☐ 37 C.F.R. § 3.73(b) Statement of Power of Attorney (when there is an assignee) 9. ☐ English Translation Document (if applicable) 10. ☐ Information Disclosure Statement (IDS)/PTO-1449 11. ☐ Preliminary Amendment 12. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized) 13. ☐ * Small Entity Statement filed in prior application, Status still proper and desired (PTO/SB/09-12) 14. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 15. ☐ Other: _____			
2. ☒ Specification [Total Pages 52] (preferred arrangement set forth below) - Descriptive title of the Invention - Cross References to Related Applications - Statement Regarding Fed sponsored R & D - Reference to Microfiche Appendix - Background of the Invention - Brief Summary of the Invention - Brief Description of the Drawings (if filed) - Detailed Description - Claim(s) - Abstract of the Disclosure	6. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary) a. ☐ Computer Readable Copy b. ☐ Paper Copy (identical to computer copy) c. ☐ Statement verifying identity of above copies				
3. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets _____]					
4. ☐ Oath or Declaration [Total Pages 4] a. ☒ Newly executed (original or copy) b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 16 completed) c. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).					
* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).					
16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment: ☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____ Prior application information: Examiner _____ Group / Art Unit: _____ For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.					
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PATENT CASE
IN01003K2

HIV THERAPY

- 5 CROSS-REFERENCE TO RELATED APPLICATIONS: This application is
a continuation-in-part of commonly-owned U.S. Patent Application SN
09/288,358, filed on April 8, 1999, which is a continuation-in-part of
commonly-owned U.S. Patent Application SN 09/268,521, filed on March
12, 1999, which is a continuation-in-part of commonly-owned U.S. Patent
10 Application SN 09/260,388, filed on March 2, 1999.

BACKGROUND OF THE INVENTION

- 15 The present invention relates to methods of treating patients having
immunodeficiency virus type-1 ("HIV-1") infections by administering a
therapeutically effective amount of pegylated interferon-alfa sufficient to
lower HIV-1-RNA .

- 20 A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy,
9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in
man including at least triple drug combinations or so-called Highly Active
Antiretroviral Therapy ("HAART") ; HAART involves various combinations
of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside
reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors
25 ("PI"). In compliant drug-naive patients, HAART is effective in reducing
mortality and progression of HIV-1 to AIDS. However, these multidrug
therapies do not eliminate HIV-1 and long-term treatment usually results in
multidrug resistance. Development of new drug therapies to provide
better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

5 The present invention provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated interferon-alfa sufficient to lower HIV-RNA.

10 The present invention also provides a method of treating patients having HIV-1 infections which comprises administering about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

15 The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 therapy in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

20 The present invention also provides a method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

25 The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering, in a second treatment time period, a therapeutically effective amount of an anti-HIV-1 therapy in association
30 with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

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5 The present invention also provides a method of treating patients having HIV-1 infections which comprises (1) administering, in a first treatment time period of about two to about four weeks, about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering, in a second treatment time period, a therapeutically effective amount of HAART in association with about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.

10 The present invention also provides a method of treating pediatric patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with pegylated interferon-alfa.

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DETAILED DESCRIPTION

20 The present method of treating patients having HIV-1 infections comprises administering a therapeutically effective amount of pegylated interferon-alfa as monotherapy or in association with a therapeutically effective amount of at least one of ribavirin, interleukin-2("IL-2"), interleukin-12("IL-12"), and pentafuside alone or in combination with an anti-HIV-1 therapy, especially, HAART, in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. See for example A-M. Vandamme et al., in Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) and "Drugs for HIV Infection" in The Medical Letter Vol. 39 (Issue 1015) December 5, 1997, pages 111-116.. The initiation of the HAART may occur before, after or concurrently with administering a therapeutically effective amount of pegylated interferon-alfa in accordance with the present invention. In an embodiment of the present invention, the method of treating patients having HIV-1 infections comprises two

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treatment time periods. In the first treatment time period, a therapeutically effective amount of pegylated interferon-alfa is administered for a first treatment time period sufficient to lower HIV-1-RNA plasma levels, by $\geq 0.5 \log_{10}$, i.e., $\geq 0.5 \times 10^1$ preferably by one $\log_{10}$, i.e., $\geq 1 \times 10^1$, more preferably by at least two $\log_{10}$, i.e., at least 10^2 , lower than the initial HIV-1-RNA plasma level. In the second treatment time period, the method entails continuing the administration of a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of HAART in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections, including when to start multidrug therapy and which drugs to combine. The triple drug therapy may include two nucleoside and nucleotide reverse transcriptase inhibitors ("NRTIs") and one protease inhibitor ("PI"), but there are many issues to be considered in the choice of the precise HAART for any patient. See for example, Tables 1 & 2 and Figure 2 in A-M. Vandamme et al., listed hereinabove.

The term "patients having HIV-1 infections" as used herein means any patient -including a pediatric patient-having HIV-1 infection and includes treatment-naive patients and treatment-experienced patients having the HIV-1 infection as well as treatment-naive patients and treatment-experienced patients co-infected with the HIV-1 and hepatitis C virus ("HCV").

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The term "pediatric patient" as used herein means a patient below the age of 17, and normally includes those from birth to 16 years of age.

The term "treatment-naive patients" as used herein means patients having HIV-1 or co-infected with the HIV-1 and HCV who have never been

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treated with any anti-retroviral drugs, e.g., NRTI, NNRTI, PI or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

5 The term "treatment-experienced" patients as used herein means those patients having HIV-1 or co-infected with the HIV-1 and HCV who have initiated some form of anti HIV therapy including, but not limited to HAART or some form of anti-HCV therapy, including but not limited to interferon-alfa, pegylated interferon alfa or ribavirin.

10 The term "patients having hepatitis C infections" as used herein means any patient-including a pediatric patient- having hepatitis C and includes treatment-naive patients having hepatitis C infections and treatment-experienced patients having hepatitis C infections as well as those pediatric, treatment-naive and treatment-experienced patients
15 having chronic hepatitis C infections.

These patients having hepatitis C include those who are infected with multiple HCV genotypes including type 1 as well as those infected with, e.g., HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV
20 genotypes.

The term "treatment-naive patients having hepatitis C infections" as used herein means patients with hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.
25

The term "treatment-experienced patients having hepatitis C infections" as used herein means patients with hepatitis C who have been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa, including relapsers and non-responder.
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The term "relapsers" as used herein means treatment-experienced patients with hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

5

The term "non-responders" as used herein means treatment-experienced patients with hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

- 10 When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated
- 15 interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), preferably in the range of about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b
- 20 administered twice a week (BIW), or is in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.25 to about 1.5 micrograms per kilogram
- 25 of pegylated interferon alfa-2b administered twice a week, or is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, most preferably is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 0.75
- 30 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week.

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When the pegylated interferon-alfa administered to pediatric patients is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), or about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week, or preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, and most preferably about 2.25 to about 2.6 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 1.125 to about 1.3 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW). In a preferred embodiment of the present invention, pediatric doses of about 0.75, about 1.5 and about 3.0 micrograms per kilogram of pegylated interferon alfa-2b are administered once a week

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated

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interferon alfa-2a administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 200 micrograms to about 250 micrograms

5 QW or the effective amount is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 100 micrograms to about 125 micrograms twice a week.

When the pegylated interferon-alfa administered to a pediatric

10 patient is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered during the treatment in accordance with the present invention, including in first treatment time period is in the range of about 50 micrograms to about 500 micrograms once a week("QW"), preferably about 300 micrograms to about 375

15 micrograms QW or the therapeutically effective amount of pegylated interferon alfa-2a administered to a pediatric patient is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 150 micrograms to about 190 micrograms once a week

20 Ribavirin is administered to the patient in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of ribavirin. The amount of ribavirin administered

25 concurrently with the pegylated interferon-alfa is from about 400 to about 1600 mg per day, preferrably about 600 to about 1200 mg/day or about 800 to about 1200 mg day and most preferably about 1000 to about 1200 mg/kg a day. The pegylated interferon-alfa dose is also preferably administered to the pediatric patient during the same period of time that

30 such patient receives doses of ribavirin. The amount of ribavirin administered to the pediatric patient concurrently with the pegylated -

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interferon-alfa is from about 8 to about 15 mg per kilogram per day, preferably about 8, 12 or 15 mg per kilogram per day, in divided doses.

Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Ribavirin may be administered orally in capsule, tablet or liquid form in association with the parenteral administration of pegylated interferon-alfa. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

15

The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NTRI" s) as used herein means nucleosides and nucleotides and analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HIVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN tradename from Glaxo-Wellcome Research

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Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON tradename from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by

5 Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Laval, Quebec H7V, 4A7, Canada; emitricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by

10 Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4(also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluorocytidine) licensed by Yale University to Vion Pharmaceuticals, New Haven CT 06511; and / DAPD, the purine nucleoside, (-)-beta-D-2,6,-diaminopurine dioxolane disclosed in EP 0656778 and licensed by Emory University and the

15 University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and lodenosine (FddA), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, a acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohoken, PA. 19428.

20

The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

25

Typical suitable non-nucleoside reverse transcriptase inhibitors include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delaviradine (BHAP, U-90152) available under the RESCRIPTOR tradename from Pharmacia & Upjohn

30 Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename

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from DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, a furopyridine-thiopyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5- (3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN(available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

Typical suitable protease inhibitors include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOUASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfnavir (AG-1343) available under the VIRACEPT tradename from Agouron -

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Pharmaceuticals, Inc., LaJolla, CA 92037-1020; amprenavir (141W94), a non-peptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543 as a 2nd-generation HIV-1 PI; and ABT-378 under development by Abbott , Abbott Park, IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020;

15 The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the triple and quadruple combination therapies called HAART.

20 Typical suitable anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from , NNRTIs and PIs ;see Talbes I, II and III, hereinafter.

25 Typical suitable HAART - multidrug combination therapies- include (a) triple combination therapies such as two NRTIs and one PI ; or (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment-naive patients, it is preferred to start anti-HIV-1 treatment with the triple

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combination therapy; the use of two NRTIs and one PI is preferred unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺ and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug, e.g., one PI or one NNRTI could be added. See the Table A hereinbelow.

Table A

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES

10 A. Triple Combination Therapies

1. Two NRTIs¹ + one PI²
2. Two NRTIs¹ + one NNRTI³

B. Quadruple Combination Therapies⁴

- 15** Two NRTIs + one PI + a second PI or one NNRTI

C. ALTERNATIVES:⁵

- Two NRTI¹
- One NRTI⁵ + one PI²
- 20** Two PIs⁶ ± one NRTI⁷ or NNRTI³
- One PI² + one NRTI⁷ + one NNRTI³

FOOTNOTES TO TABLE A

- 25** 1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine; See also Table I
2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules. Ritonavir is used less frequently because of troublesome adverse effects. The old formulation of saquinavir was used least often
- 30** because of its poor bioavailability and limited effectiveness, but the

new saquinavir formulation should be more effective. See also Table III.

3. Nevirapine or delavirdine. See also Table II
4. See A-M. Vandamme et al Antiviral Chemistry + Chemotherapy
5 9:187 at p 193-197 and Figures 1 + 2.
5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV-
10 resistance and clinical failure in many patients.
6. Most data obtained with saquinavir and ritonavir (each 400 mg bid). See also Table III
7. Zidovudine, stavudine or didanosine. See also Table I
- 15 Other anti-HIV-1 drugs useful for administration in association with pegylated interferon alfa include hydroxyurea, ribavirin, IL-2 and IL-12, and Yissum Project No. 11607. These above-listed anti-HIV-1 drugs may also be administered in association with pegylated interferon alfa in association with any anti-HIV-1 drug therapy, especially the triple and
20 quadruple drug combinations called HAART.

Hydroxyurea (Droxia) is a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells. Hydroxyurea discovered at the NCI is under development by Bristol-Myers Squibb. In
25 preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine.

Yissum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein under preclinical development by Yissum Research
30 Development Co., Jerusalem 91042, Israel.

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The pegylated inteferon alfa, PEG₁₂₀₀₀-IFN-alfa2b(available from Schering-Plough Research Institute, Kenilworth, NJ) increased the in vitro anti HIV-1 activity of ribavirin. The combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited HIV replication in vitro using phytohemagglutinin ("PHA" - P) - activated peripheral blood mononuclear cells ("PBMCs") at doses corresponding to plasmatic concentrations observed in animals and man. Healthy PBMCs were separated from a buffy-coat of one HIV-seronegative blood donor by Ficoll-Hypaque density gradient centrifugation. PBMCs were activated by 1 µg/ml phytohemagglutinin (PHA-P) for two days in cell culture medium A: RPMI 1640 supplemented with 10% heat-inactivated (+56°C, 45 min.) fetal calf plasma (FCS), 2 mM L-glutamine and a tri-antibiotic mixture (penicillin, streptomycin, neomycin; PSN). After these two days, cells were washed and cultured at one million cell per milliliter in cell culture medium B: cell culture medium A supplemented with 20 IU/ml recombinant human interleukin-2. Cells were maintained at +37°C in a 5% CO₂-air humidified atmosphere. Experiments were repeated twice with cells of other blood donors. In total, three independent experiments were performed.

PBMCs were infected with 1,000 50% Tissue Culture Infectious Doses (TCID₅₀) of the reference HIV-1-LAI strain [F.Barre'-Sinoussi, Science, 1983, 220, 868-871]. This strain has been amplified using PHA-P-activated umbilical blood mononuclear cells (UBMC). Viral stock has been then titrated on PHA-P activated PBMC by end-point dilution. TCID₅₀ was then calculated using Karber's formula [Arch. Exp. Path. Pharmac., 1931, 162, 126-133].

PEG₁₂₀₀₀-IFN-α2b and ribavirin, alone and in combination, and AZT used as a control, were administrated 24 hours before HIV-1 infection and

maintained all along the culture. Three doses of PEG₁₂₀₀₀-IFN- α 2b and ribavirin were used.

200,000 PHA-P-activated PBMCs were added to each well of 96-well microplates. Cells were 24 hour-pretreated prior to infection with the reference HIV-1-LAI strain. Twice a week, cell supernatants were collected, and drugs and medium were renewed. At day 7, RT activity were determined in cell supernatants, and potential cytotoxic effects of drugs and drug combinations were evaluated by microscopic observation.

Viral replication was measured by determining reverse transcriptase ("RT") activity in cell supernatants using Retro-Sys® kit, according to manufacturer's recommendations (Innovagen, Lund, Sweden).

Effective doses were calculated using cumulative RT activities with Chou J. and TC. microcomputer software.

The combined effects were analyzed using either the combination index (CI) [Chou & Talalay, 1984] with J and TC Chou microcomputer software, or the fractionary inhibitory concentration (FIC) index [Antimicrob. Agents. Chemother., 1987, 31, 1613-1617]. When the CI or FIC index is equal to 1, the combination is additive. When it is below 1.0, the combination is synergistic, and when it is above 1.0, the combination is judged as antagonistic.

PEG₁₂₀₀₀-IFN- α 2b as well as the combination of PEG₁₂₀₀₀-IFN- α 2b and ribavirin inhibited the HIV replication at doses corresponding to plasmatic concentrations measured in mice and HIV-1 infected patients

[BE. Gilbert, et al. Antimicrob. Agents Chemother., 1988, 32, 117-121; E. Connor et al., Antimicrob. Agents Chemother., 1993, 37, 537-539].

IL-2 is disclosed in Ajinomoto EP-0142268, Takeda EP-0176299,
5 and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377,
4748234, 4752585, and 4949314 is available under the
PROLEUKIN(aldesleukin) tradename from Chiron Corp., Emeryville, CA
94608-2997 as a lyophilized powder for IV infusion or sc administration
upon reconstitution and dilution with water; doses of about 1 to about 20
10 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is
more preferred.

IL-12 is disclosed in WO96/25171 and is available from Roche
Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products,
15 Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10
microgram/kg/day, sc.

Pentafuside (DP-178, T-20) a 36-amino acid synthetic
peptide, disclosed in U.S. Patent No. 5,464,933 licensed from Duke
20 University to Trimeris which is developing pentafuside in collaboration with
Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target
membranes. Pentafuside (3-100 mg /day) is given as a continuous sc
infusion or injection together with efavirenz and 2 PI's to HIV-1 positive
patients refractory to a triple combination therapy; use of 100 mg/day is
25 preferred.

The term " interferon-alfa " as used herein means the family
of highly homologous species-specific proteins that inhibit viral replication
and cellular proliferation and modulate immune response. Typical suitable
30 interferon-alfas include, but are not limited to, recombinant interferon alfa-
2b such as Intron-A interferon available from Schering Corporation,

Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a
5 purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product
10 available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval
15 throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

The term "pegylated interferon alfa" as used herein means
20 polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG₁₂₀₀₀-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG₁₂₀₀₀-IFN alfa" as used herein mean conjugates such as are prepared
25 according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

30 The preferred PEG₁₂₀₀₀-interferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN

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alfa-2b molecule. A single PEG₁₂₀₀₀ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG₁₂₀₀₀ attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human plasma albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosol, cresol or benylalcohol), and surfactants(e.g. tween or polysorabates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used

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within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes
5 include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa
10 powder in a separate compartment.

A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

- 15 (a) elevated ALT,
- (b) positive test for anti-HCV antibodies,
- (c) presence of HCV as demonstrated by a positive test for the
20 presence of HCV-RNA in the serum,
- (d) clinical stigmata of chronic liver disease,
- (e) hepatocellular damage.

25 To practice the invention, the combination therapy of pegylated interferon-alfa and ribavirin is administered in association with anti-retroviral therapy, e.g., HAART, to the patient having HIV-1 infection and exhibiting one or more of the above signs or symptoms in the first and
30 second treatment time periods in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms., and to lower the HCV-

RNA serum levels by at least a power of ten, and preferably to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period. The sum of the first and
5 second treatment time periods is about 40-50 weeks, and preferably is 48 weeks. Administration of the ribavirin may be discontinued after the end of the second time period depending upon the judgment of the attending clinician.

The term "no detectable HCV-RNA" in the context of the present
10 invention means that there are fewer than 100 copies of HCV-RNA per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-
15 RNA/qPCR. The lower limit of detection of HCV-RNA is 100 copies/mL. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

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In a preferred embodiment of the present invention, those patients co-infected with HIV-1 and HCV infections are treated with pegylated interferon alfa in combination with ribavirin and a HAART combination considered appropriate by the attending clinician and the patient; use of
25 the interferon alfa-2b-ribavirin combination therapy sold by Schering Corp. under the REBETRON tradename is preferred. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499). Ribavirin, 1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN
30 Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

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For the pediatric patient co-infected with the H IV-1 and HCV infections, a suitable HAART includes a NRTI+ a PI, e.g., Nelfinavir +a NNRTI, e.g., Efavirenz in combination with the dosages and dosage regimens for pegylated interferon alfa and ribavirin listed herein above. See also Tables I-IV herein below. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may be administered to these pediatric patients in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician to reduce retardation of growth associated with pegylated interferon alfa treatment.

HAART is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose may be administered before, after or during the same period of time that the patient receives doses of HAART. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may also be administered -in association with HAART and pegylated interferon alfa - to the pediatric patient having HIV-1 infection in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician.

In a preferred embodiment of the present invention, pegylated interferon alfa is administered to HIV-1 infected patients prior to initiation of HAART, and preferably about two to about four weeks prior to initiation of HAART. In another preferred embodiment of the present invention, administration of pegylated interferon alfa is initiated concurrently, i.e., on the same day with the administration of HAART. In another preferred

embodiment of the present invention the pegylated interferon-alfa is administered after the HIV-1 infected patient has initiated HAART.

The goal of the anti-HIV-1 therapy of the present invention is to
5 reduce the HIV-1-RNA viral load below the detectable limit. The
“detectable limit of HIV-1-RNA” in the context of the present invention
means that there are fewer than about 200 to fewer than about 50 copies
of HIV-1-RNA per ml of plasma of the patient as measured by quantitative,
multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is
10 preferably measured in the present invention by the methodology of
Amplicor -1 Monitor 1.5 (available from Roche Diagnostics) or of Nuclisens
HIV-1 QT - 1. This methodology is described by Schooley, RT, Antiviral
Therapy(1997), 2 (Suppl. 4):59-70.

15 The doses and dosage regimen of the NRTIs, NNRTIs and PI; IL-2,
IL-12 and pentafuside will be determined by attending clinician in view of
the approved doses and dosage regimen in the package insert or as set
forth in the protocol taking into consideration the age, sex and condition of
the patient and the severity of the HIV-1 infection. For the pediatric patient
20 infected with the HIV-1, or co-infected with the HIV-1 and HCV infections
a suitable HAART includes a NRTI+ a PI, e.g., Nelfinavir
+a NNRTI, e.g., Efavirenz in combination with the dosages and dosage
regimens for pegylated interferon alfa and ribavirin listed herein above.
See also Tables I-IV hereinafter for dosages and dosage regimens.

25 The following clinical protocols may be used to administer the anti-
HIV-1 therapy of the present invention. Many modifications of this clinical
protocol will be obvious to the skilled clinician, and the following Study
Designs should not be interpreted as limiting the scope of the method of
30 this invention which is only limited by the claims listed hereinafter. See for

example J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

5

STUDY NO. 1

The study population will include male and female patients diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced and will be included if they meet the following inclusion and exclusion criteria:

10

Subject Inclusion Criteria:

- Subjects diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced.
- HIV-RNA by Amplicor test, Version 1.5 of greater than 500 copies/mL.
- CD₄ + count greater than 100 copies/ml, preferably greater than 200 cells/mL.
- Subjects in good physical health with clinically acceptable safety laboratory test results and ECG.
- The following laboratory parameters must be met:
 - ◆ Platelet count •100,00/mL
 - ◆ Hemoglobin •9 gm/dL (90 gm/L)
 - ◆ Absolute neutrophil count •1500/ μ L
 - ◆ Creatinine $\angle$ 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT $\leq$ 5 x upper limit of normal
 - ◆ Bilirubin $\leq$ 2.5 x upper limit of normal
- A negative urine pregnancy test (females only)

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Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.

Subject Exclusion Criteria

- Females who are breast-feeding or pregnant or who are not using adequate birth control.
- 5 • Subject with allergy to E. coli proteins
- Subjects with a significant past medical/psychiatric history, specifically depression or dementia.

The subjects will be randomized to receive pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b at doses between 0.5 and 4.5 micrograms per kilogram e.g. at doses of 0.5, 1.0, 1.5, 3.0 or 4.5 micrograms per kilogram by subcutaneous injection once a week. HAART may also be initiated before or concurrently with the administration of the pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b, i.e., PEG-
15 Intron which is available from Schering Corp, Kenilworth, NJ.

Overall Design and Plan of the Study:

The primary efficacy objective will be lowering of the HIV-I-RNA plasma levels by a factor of $\geq 0.5 \log_{10}$.

Plasma HIV-1-RNA/qPCR testing will be performed by a central laboratory. A positive HIV-1-RNA assay result will be required at Baseline; only patients positive for HIV-1-RNA will be eligible to participate.

25

STUDY NO. 2**Study Objectives**

The objectives of this study are to investigate: (i) the antiviral activity of various-doses of PEG-Intron in treatment-experienced, HIV-1
30 infected subjects failing their current anti-retroviral(anti-HIV-1) regimen, (ii) the antiviral activity of PEG-Intron in subjects starting a new optimized

HAART regimen after failing their previous regimen and (iii) the safety, tolerability and pharmacokinetics of PEG-Intron.

Study Design

- 5 This is a Phase II, randomized, double-blind, parallel group, placebo-controlled, multi-center, efficacy and safety study in treatment-experienced HIV-1 infected subjects. Individuals who achieve $\geq 0.5 \log_{10}$ reduction in HIV RNA at Week 4 will continue their PEG-Intron regimen with the addition of new optimized HAART for an additional 24 weeks. All
- 10 other patients will be discontinued but will be asked to return for follow-up viral load and lymphocyte subset studies at Week 16 and Week 28. Subjects who were randomized to the placebo arm will be offered compassionate use of PEG-Intron when the optimal dose of PEG-Intron has been determined.

15

Duration of Study

PEG-Intron will be administered subcutaneously once per week for up to 28 weeks. There will be a 4 week post-treatment follow-up period.

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Study Population

- The study population will include a total of 300 male and female subjects with documented HIV-1 infection who have been treated continuously with combination antiretroviral therapy for at least six months prior to study entry. As a general guideline, patients should be in
- 25 reasonably good health with a Karnofsky Performance Scale score ≥ 70 . Patients must meet the Inclusion and Exclusion Criteria listed below.

Subject Inclusion Criteria

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- Documentation of HIV-1 infection by any licensed ELISA test kit and confirmed by a second method (e.g., Western Blot); or by HIV culture, HIV p24 antigen, plasma HIV RNA or proviral DNA.
 - Subjects ≥ 18 years old who have been on a continuous HAART regimen for at least six months, prior to randomization; and on the current regimen for at least 6 weeks.
 - HIV-RNA increase ≥ 3 -fold ($0.5 \log_{10}$) from previous nadir in the last 6 months using the same assay; or a previous plasma HIV RNA level < 500 copies/mL on current antiretroviral regimen.
 - HIV-RNA $\geq 2,000$ copies/mL using same assay, on 2 separate occasions (at least 7 days apart) prior to starting study drug.
 - CD_4^+ cell count ≥ 200 cells/mL.
 - Absence of active systemic opportunistic infection.
 - The following laboratory parameters must be met:
 - ◆ Platelet count $\geq 100,000/\text{mm}^3$
 - ◆ Hemoglobin $\geq 9\text{gm/dL}$
 - ◆ Absolute neutrophil count $\geq 1,500/\text{mm}^3$
 - ◆ Creatinine ≥ 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT ≥ 5 times the upper limit of normal
 - A negative serum pregnancy test (females of childbearing potential only).
 - Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.
- Subject Exclusion Criteria**
- Ongoing Intron or PEG-Intron therapy within the last 6 months.
 - Females who are breast-feeding or pregnant or of childbearing potential and not using adequate birth control measures, e.g. intrauterine medroxyprogesterone acetate [Depro-Provera], surgical

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sterilization, oral contraception, barrier method [diaphragm + spermicide or condom], during the treatment period.

- Individuals currently participating in, or who have participated in, a clinical trial of an investigational drug in the previous month.
- 5 • Subjects with a history of hypersensitivity to Interferons.
- Subjects with a history of severe depression, dementia, or other major psychiatric illness.
- Any CNS abnormality that requires use of antiseizure medication.
- Unwillingness or inability to change to new optimized HAART.
- 10 • Unwillingness to wait until HIV resistance profile is available before changing current antiretroviral regimen.
- Intercurrent illness, vaccinations, or use of immunomodulators (within 2 weeks prior to randomization) that could influence the plasma HIV RNA level.
- 15 • Use of systemic corticosteroids (excluding anabolic agents), immunosuppressants, ribavirin, or cytotoxic agents (including hydroxyurea) within 2 weeks prior to randomization.

- In addition, study drug will be stopped and subjects will be
- 20 discontinued from the study in the following situations: Baseline evaluations outside the range permitted by the protocol; failure to achieve at least 0.5 log₁₀ reduction in HIV RNA at Week 4; use of a medication excluded by the protocol; subject enrollment in another investigational drug trial at any time during the study; medically serious or life threatening
- 25 adverse events; protocol defined virologic failure; pregnancy during the treatment phase; failure to comply with dosing (as defined by protocol); subject unwillingness to continue.

Method of Treatment Assignment (Randomization)

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Subjects who meet the criteria for entry will be randomly assigned to one of five treatment groups in a 1:1:1:1:1 ratio.

Study Treatments

5 Subjects will be randomized to one of the 5 following treatment groups:

- PEG-Intron 0.5 µg/kg once weekly SC
- PEG-Intron 1 µg/kg once weekly SC
- PEG-Intron 1.5 µg/kg once weekly SC
- 10 • PEG-Intron 3 µg/kg once weekly SC
- PEG-Intron placebo once weekly SC

15 All injections of PEG-Intron to be used in this study will be prepared not more than 24 hours prior to administration (provided the dose is kept refrigerated). PEG-Intron is supplied by Schering Corp. , Kenilworth, NJ 07033 as a lyophilized powder, and should be prepared as follows:

20 From a vial/ampule of Sterile Water for Injection, withdraw 0.7 mL with a syringe (1/2 inch, 27 gauge needle on a 1.0 mL syringe). Add the sterile water to the vial containing the PEG-Intron lyophilized powder and mix gently. Inspect vial for discoloration or particulate matter and discard if present. On Day 1 of each week, PEG-Intron will be injected subcutaneously with the injection sites being rotated as necessary. Patients will receive one injection per week of PEG-Intron or placebo for up to 52 weeks.

25

Administration of Study Medication

- PEG-Intron/Placebo - Dosing will be calculated on a µg/kg basis using the Baseline visit weight and will be administered (SC) subcutaneously. Subjects will administer PEG-Intron on the same day of the week each week.

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Subjects may receive acetaminophen (500-1000 mg) 30 minutes prior to receiving PEG-Intron.

5 **Primary Endpoints**

The primary endpoint will be the average change in HIV RNA from Baseline to Week 4 of PEG-Intron therapy. Baseline HIV RNA will be the mean of 2 RNA values, one obtained 7-14 days prior to starting study drug and the other obtained immediately prior to the first dose of study drug.

10

Secondary Endpoints

Secondary endpoints include the following: AUC for HIV RNA from Baseline to Week 4; change in CD₄ + absolute count and percent from Baseline to Week 4; change in markers of T cell activation from Baseline to Week 4. In addition, the following parameters will be studied: change in viral load (and AUC) at Weeks 12, and 24 after starting new optimized HAART; change in CD₄ + absolute count and percent at 12 and 24 weeks after new optimized HAART; time to HIV RNA decline below limit of quantitation of assay after starting new HAART; and change in HIV resistance profile of the individual components of each subject's HAART regimen at 24 weeks after new optimized HAART or at the time of virologic failure (whichever occurs first).

25 **Laboratory Evaluations**

A central laboratory will be used for clinical laboratory testing during the study. Baseline results from the central laboratory will be used as a basis for determining whether a clinically significant change has occurred in a safety variable after the first dose of study medication. If necessary, additional laboratory assessments needed for subject safety during the

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STUDY NO. 3

Study Objectives

The objectives of this rising multiple-dose, open-label study are: (1) to assess the safety and tolerability of single and multiple doses of PEG-Intron in chronically HIV-infected pediatric patients who may have resistance to ongoing oral antiretroviral therapy, using a rising dose study design; (2) to measure the single and multiple dose pharmacokinetics of PEG-Intron in chronically HIV-infected pediatric patients; and (3) to examine the effect of PEG-Intron on HIV viral pharmacodynamics (HIV-RNA, CD₄⁺ counts) and immune parameters.

15

Study Design

This is a Phase I, open-label, rising multiple-dose, uncontrolled, multi-center, safety, tolerability, pharmacokinetic and pharmacodynamic study, in chronically HIV-1 infected pediatric subjects. This study is also designed to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of PEG-Intron in children when given once weekly for 4 weeks.

Duration of Study

Study treatment will be administered once per week for 4 weeks.

Study Population

6mo. Twenty-seven male and/or female HIV-infected pediatric patients aged 1-16 years will be enrolled into this study. Patients must have chronic HIV infection for >1 year. Patients must be established on

12/3/95
12/3/95
12/3/95
6 mos.

antiretroviral therapy with detectable (>500 copies/mL) serum HIV-RNA titers. No change in antiretroviral regimen will be allowed within 6 weeks of study entry or while receiving PEG-Intron. Patients must meet the Inclusion and Exclusion Criteria listed below.

5

Subject Inclusion Criteria

Subjects should be generally in good physical health with clinically acceptable safety laboratory test results and normal ECG.

- 10
- Subjects between the ages of ~~2~~ ^{12/2/88} and 16 years, with chronic HIV-I infection on a stable antiretroviral regimen for at least 6 weeks. Subjects must remain on their antiretroviral regimen for the duration of the study.
- 15
- HIV-RNA levels as determined by Amplicor of greater than 500 copies/mL.
 - %CD₄⁺ counts greater than 200 cells/mL (CDC Immunologic Category 1 or 2).
 - Absence of active systemic opportunistic infection on physical examination.
- 20
- No history of systemic opportunistic infection or immunization within the preceding 2 months
 - The following laboratory parameters must be met:
 - ◆ Platelet count $\geq 100,000/\mu\text{L}$ ($100 \times 10^9/\text{L}$)
 - ◆ Hemoglobin $\geq 9 \text{ gm/dL}$ (90 gm/L)
- 25
- ◆ Absolute neutrophil count $\geq 1500/\mu\text{L}$ ($0.15 \times 10^9/\text{L}$)
 - ◆ Creatinine < 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT ≤ 5 x upper limit of normal
 - ◆ Bilirubin ≤ 2.5 x upper limit of normal
 - A negative serum pregnancy test (females only).

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- 5
- Parents/guardians must provide written informed consent, children capable of doing so will also given written informed consent. At minimum children must provide verbal agreement to participate. All participants must be able to adhere to the schedule set forth in the protocol.

Subject Exclusion Criteria

- 10
- Subjects with clinically significant disorders not related to their HIV disease.
 - Progression of HIV-I to AIDS.
 - Females who are breastfeeding or pregnant or who are not using adequate birth control.
 - Individuals who have participated in a clinical trial of an investigational drug in the previous month.

15

 - Subjects who are positive for hepatitis B surface antigen or hepatitis C antibody.
 - Subjects with allergy to E. coli proteins.
 - Subjects with a significant past medical/psychiatric history, specifically depression.

20

 - Presence of Interferon neutralizing antibodies (these results may not be available during screening; patients will be considered for Inclusion without these results).
 - Patients with clinical history of drug dependence.

25 **Method of Treatment Assignment (Randomization)**

Patient numbers will be centrally assigned. Treatment allocation will not be randomized in this study.

Twenty-seven subjects will receive PEG-Intron at doses of 0.75, 1.5 or 3.0 $\mu\text{g/kg}$ by subcutaneous injection once per week(QW) for 4 weeks.

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The first nine patients will be enrolled at the 0.75 $\mu\text{g/kg}$ dose level. Subsequent cohorts of nine patients will be enrolled at successively higher doses according to the dose escalation guidelines below. Enrollment of the 1.5 $\mu\text{g/kg}$ QW dose group can begin after all subjects in the 0.75 $\mu\text{g/kg}$

- 5 QW dose level have received at least two weeks of PEG-Intron therapy without any subject having experienced a dose limiting toxicity (DLT). Enrollment of the 3.0 $\mu\text{g/kg}$ QW dose group can begin after all subjects in the 1.5 $\mu\text{g/kg}$ QW have received at least two weeks of PEG-Intron therapy without any subject having experienced a dose limiting toxicity (DLT). If
- 10 any of the subjects at any level experiences DLT at anytime during the first 2-week treatment period, enrollment into the next higher dose level will be postponed until all subjects complete four weeks of treatment and do not experience further DLT. The DLT level will be defined when two subjects at any dose level experience DLT. The next lower dose will be
- 15 considered the maximum tolerated dose (MTD).

Stratification

Within each dose level (n=9) at least 3 patients enrolled must be <10 years, and at least 3 patients must be ≥ 10 years.

20

Study Treatments

- PEG- Intron :0.75, 1.5 or 3.0 $\mu\text{g/kg}$ SC, QW.

All injections of PEG-Intron to be used in this study will be prepared not more than 24 hours prior to administration (provided the dose is kept refrigerated). PEG-Intron is supplied as a

25 lyophilized powder, and should be prepared as follows:

From a vial of Sterile Water for Injection, withdraw 0.7 mL with a syringe (5/8 inch, 25 gauge needle on a 1.0 mL syringe). Add the sterile water to the vial containing the PEG-Intron

30 lyophilized powder and mix gently. Inspect for discoloration or

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particulate matter. If present, discard vial. 0.5 mL of this solution contains 50 μ g, 100 μ g or 150 μ g of PEG- Intron depending on the vial used. On Day 1 of each week, PEG- Intron will be injected subcutaneously with the injection sites being rotated as necessary.

5 Patients will receive one injection per week for 4 weeks.

Dosing volumes will be calculated using the following formula:

10
$$\text{Volume} = \text{body-weight} \times \text{dose/PEG-Intron concentration}$$

- For the 0.75 μ g/kg dose, using a 50 μ g vial size:

$$\text{Volume (mL)} = \text{body-weight (kg)} \times 0.75 \mu\text{g/kg}/100 \mu\text{g/mL}$$

- For the 1.5 μ g/kg dose, using a 100 μ g vial size:

15
$$\text{Volume (mL)} = \text{body-weight (kg)} \times 1.5 \mu\text{g/kg}/200 \mu\text{g/mL}$$

- For the 3.0 μ g/ml dose, using a 150 μ g vial size:

$$\text{Volume (mL)} = \text{body-weight (kg)} \times 3.0 \mu\text{g/kg}/300 \mu\text{g/mL}$$

20 All doses of PEG- Intron must be administered at the clinic under the direction of the study staff.

During the first 48 hours of therapy, the study physician, physician coordinator or nursing staff should be easily accessible to the subject since adverse events are typically the most severe following the first
25 injection. Flu-like symptoms, fever, chills, fatigue and malaise may occur in subjects two to eight hours after the initial dose of study medication. Initial reactions are generally mild to moderate in nature, and in most subjects tachyphylaxis of these symptoms will occur.

For patients who complete all Week 4 procedures, and who in the
30 opinion of the Investigator might benefit from continued treatment, PEG-

Intron treatment may be continued post-study in a continuation study. During compassionate treatment, there will be monitoring of safety, tolerability, virology and immunological parameters by the Principal Investigator.

5

Primary Endpoints

The following are primary endpoints:

- Safety laboratory tests, vital signs, ECGs and reported adverse events during 4 weeks of treatment.
- 10 • Serum HIV-RNA titer and CD₄⁺ cell counts during 4 weeks of treatment.
- Single and multiple-dose serum PEG-Intron concentrations (Weeks 1 and 4).

15

The primary objective of this study is to describe the safety and tolerability of PEG- Intron based on data from the 4 weeks of treatment. Concentration data and derived pharmacokinetic parameters (AUC and Cmax) of PEG-Intron, and HIV-RNA titers will be summarized using descriptive statistics. In addition to the analyses specified below, listings of all data for each patient will be provided.

20

Pretreatment (Days -28, -2 and Day 1, 0 hour) HIV-RNA and CD₄⁺ counts will be used as Baselines for each individual. Relative to mean Baseline value, evidence of Interferon response will be based on >0.5 log reduction in HIV-RNA.

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Footnotes Table I

* Available in a liquid formulation.

1 For patients less than 60 kg, 30 mg PO bid.

40 2 With tablets; for patients < 60 kg, 125 mg PO bid; ≥60 kg, 200 mg PO bid;. With powder, dosage varies from 167 mg (< 60 kg) to 250 mg PO (< 60 kg) bid. Doses should be taken at least 30 minutes before meals or at least two hours afterward.

3 For patients less than 50 kg, 2 mg/kg PO bid.

4 Each tablet contains 300 mg of zidovudine and 150 mg of lamivudine.

45 5 Available under an expanded access program - a NIH-sponsored Phase III Trial

6 Phase II

Table 1 Footnotes continued

- 7 Phase I/II; see PharmaProjects, sections J5A & J5Z
5 8 Phase II/III; see PharmaProjects, sections J5A & J5Z
9 Preclinical; active in duck HBV model; see PharmaProjects, sections J5A & J5Z
10 Preclinical; active po and IV; DAPD is a prodrug of another dioxolene purine, DXG. See
PharmaProjects, sections J5A & J5Z
11 Phase II, FddA has potential for once-a-day dosage
10

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TABLE II

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

NRTI (Tradename, Marketer)		Usual adult dosage and Dosage Regimen
5	Nevirapine (Viramune - Roxane)	200 mg PO bid ¹
10	Delavirdine (Rescriptor - Pharmacia & Upjohn)	400 mg PO tid
	Efavirenz (Sustiva, Dupont)	200 mg PO qid ²
15	PNU-142721 (Pharmacia + Upjohn)	_____ ³
	AG-1549 (Agouvon Pharmaceuticals)	_____ ⁴
	MKC-442 (Triangle Pharmaceuticals)	750 mg PO bid ⁵
20	(+)-Calanolide A (Med Chem Research)	800 mg PO ⁶

1 For the first two weeks of treatment with nevirapine, to decrease the risk of rash, patients
25 should take only one 200-mg tablet per day.
2 Quadruple Therapy of efavirenz with indinavir + 2 NRTIs or Triple Therapy of efavirenz +
AZT + lamivudine.
3 Preclinical Phase; see PharmaProjects, sections J5A & J5Z
4 Phase I/II evaluating dose and concomitant use with other anti-HIV-1 therapies; see
30 PharmaProjects, sections J5A & J5Z.
5 Triple Therapy of (a) MKC-442 with stavudine and either lamivudine or didanosine or (b)
MKC-442 with nelfinavir (qv) and NRTIs.
6 Phase I; see PharmaProjects, sections J5A & J5Z

1. The first part of the document is a list of names and their corresponding addresses. The names are listed in a column on the left, and the addresses are listed in a column on the right. The names are: John Doe, Jane Smith, Robert Brown, Mary White, and David Black. The addresses are: 123 Main St, New York, NY 10001; 456 Elm St, New York, NY 10002; 789 Oak St, New York, NY 10003; 101 Pine St, New York, NY 10004; and 202 Cedar St, New York, NY 10005.

2. The second part of the document is a table with two columns. The first column is labeled "Name" and the second column is labeled "Address". The table contains the same data as the first part of the document.

Name	Address
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Jane Smith	456 Elm St, New York, NY 10002
Robert Brown	789 Oak St, New York, NY 10003
Mary White	101 Pine St, New York, NY 10004
David Black	202 Cedar St, New York, NY 10005

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Robert Brown	789 Oak St, New York, NY 10003
Mary White	101 Pine St, New York, NY 10004
David Black	202 Cedar St, New York, NY 10005

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Mary White	101 Pine St, New York, NY 10004
David Black	202 Cedar St, New York, NY 10005

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8. The eighth part of the document is a table with two columns. The first column is labeled "Name" and the second column is labeled "Address". The table contains the same data as the first part of the document.

Name	Address
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Robert Brown	789 Oak St, New York, NY 10003
Mary White	101 Pine St, New York, NY 10004
David Black	202 Cedar St, New York, NY 10005

9. The ninth part of the document is a list of names and their corresponding addresses. The names are listed in a column on the left, and the addresses are listed in a column on the right. The names are: John Doe, Jane Smith, Robert Brown, Mary White, and David Black. The addresses are: 123 Main St, New York, NY 10001; 456 Elm St, New York, NY 10002; 789 Oak St, New York, NY 10003; 101 Pine St, New York, NY 10004; and 202 Cedar St, New York, NY 10005.

10. The tenth part of the document is a table with two columns. The first column is labeled "Name" and the second column is labeled "Address". The table contains the same data as the first part of the document.

Name	Address
John Doe	123 Main St, New York, NY 10001
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Robert Brown	789 Oak St, New York, NY 10003
Mary White	101 Pine St, New York, NY 10004
David Black	202 Cedar St, New York, NY 10005

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767**TABLE III****Protease Inhibitor (PI) Dosage and Dosage Regimen**

5	PI (Tradename, Marketer)	Dosage + Dosage Regimen
	Saquinavir (Invirase - hard gel capsule- Roche)	600 mg PO tid ¹
	(Fortovase - soft gel capsule -Roche)	1100 mg PO tid ¹
10	Ritonavir (Norvir - Abbott)	600 mg PO bid ²
	Indinavir (Crixivan - Merck)	800 mg PO qid ³
	Nelfinavir (Viracept - Agouron)	750 mg PO tid ⁴
15	Amprenavir (141W94, Glaxo)	900 mg - 1200 mg PO bid ⁵
	Lasinavir (BMS-234475, BMS)	_____ ⁶
20	DMP-450 (Triangle Pharmaceuticals)	_____ ⁷
	BMS-2322623 (BMS)	_____ ⁸
	ABT-378 (Abbott)	60 mg PO bid ⁹
25		
	¹	With, or within two hours after, a full meal.
	²	With food. The liquid formulation has an unpleasant taste; the manufacturer suggests taking it with chocolate milk or a liquid nutritional supplement.
30	³	With water, one hour before or two hours after a meal. Patients taking indinavir should drink at least 48 ounces (1.5 liter) of water daily.
	⁴	With food.
	⁵	Quadruple Combination Therapy of amprenavir with AZT + lamivudine + abacavir.
	⁶	Phase I/II; see Pharmaprojects, sections J5A & J5Z.
35	⁷	Phase II; see Pharmaprojects, sections J5A & J5Z.
	⁸	Preclinical Studies; Prodrug esters of BMS 2322623 enhance oral absorption; see Pharmaprojects, sections J5A & J5Z.
	⁹	Phase I Studies show ABT-378 to be 10X more potent than ritonavir; see Pharmaprojects sections J5A & J5Z.
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Other Anti-HIV-1 Drugs

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We claim:

1. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of pegylated
5 interferon-alfa sufficient to lower detectable HIV-1-RNA.
- 2 The method of claim 1, wherein the patients are treatment-naive patients.
- 10 3. The method of claim 1, wherein the patients are treatment-experienced patients.
- 4 The method of claim 1, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a or pegylated interferon alfa-
15 2b.
5. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to
20 about 9.0 micrograms per kilogram per week.
6. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to
25 about 3.0 micrograms per kilogram per week.
- 7 . The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to
30 about 1.5 micrograms per kilogram per week.

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8. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b.
- 5 9. The method of claim 1 wherein the pegylated interferon alfa-2b is administered in association with an anti-HIV-1 drug therapy.
10. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the pegylated
10 interferon alfa-2b is administered in association with HAART.
11. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of
15 pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms per week.
12. The method of claim 1, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of
20 pegylated interferon alfa-2a administered is in the range of about 200 to about 250 micrograms per week.
13. A method of treating patients having HIV-1 infections which comprises administering about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b per week.
25
14. . The method of claim 13, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram QW.
- 30 15. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective

amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

- 5 16. The method of claim 15 wherein the anti-HIV-1 drug therapy is HAART.

- 10 17. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

- 15 18. The method of claim 17 wherein the anti-HIV-1 drug therapy is HAART.

- 20 19. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered QW for at least about 2 to 4 weeks prior to administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

20. The method of claim 19 wherein the anti-HIV-1 drug therapy is HAART.

- 25 21. The method of claim 13, wherein the pegylated interferon-alfa-2b is administered after administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.

- 30 22. The method of claim 21, wherein the anti-HIV-1 drug therapy is HAART.

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23. A method of treating patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa 2b per week.
24. The method of claim 23, wherein the an anti-HIV-1 drug therapy is HAART.
25. The method of claim 23, wherein the patients are treatment-naive patients.
26. The method of claim 23, wherein the patients are treatment-experienced patients.
27. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram in a single dose QW or divided doses BIW
28. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram in a single dose QW or divided doses BIW
29. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, and pentafuside alone or in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.
30. The method of claim 29, wherein the an anti HIV-1 drug therapy is HAART.

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31. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered in association with administering a therapeutically effective amount of ribavirin, in combination with a therapeutically effective amount of an anti HIV-1 drug therapy.

32. The method of claim 31, wherein the an anti HIV-1 drug therapy is HAART.

33. The method of claim 31, wherein the patient is co-infected with HCV.

34. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 3.0 micrograms per kilogram in a single dose QW .

35. The method of claim 34, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.25 to about 1.5 micrograms per kilogram BIW.

36. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.75 to about 1.5 micrograms per kilogram in a single dose QW .

37. The method of claim 36, wherein the amount of pegylated interferon alfa-2b administered is about 1.5 micrograms per kilogram in a single dose QW.

38. The method of claim 23, wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.375 to about 1.5 micrograms per kilogram BIW.

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39. The method of claim 23, wherein the pegylated interferon-alfa-2b is administered to a patient co-infected with HCV in association with administering a therapeutically effective amount of ribavirin, in combination with a therapeutically effective amount of HAART.

40. A method of treating patients having HIV-1 infections which comprises (1) administering in a first treatment time period of at least about two to about four weeks about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon-alfa-2b per week, followed by (2) administering in a second treatment time period, a therapeutically effective amount of an anti HIV-1 drug therapy in association with about 0.1 to about 9.0 per micrograms per kilogram of pegylated interferon-alfa-2b per week.

41. The method of claim 40, wherein the an anti HIV-1 drug therapy is HAART.

42. The method of claim 40, wherein about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

43. The method of claim 40, wherein about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

44. The method of claim 40, wherein about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week is administered in each time period.

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45. The method of claim 40, wherein the patients are treatment-naive patients.

46. The method of claim 40, wherein the patients are treatment-experienced patients.

5

47. A method of treating pediatric patients having HIV-1 infections which comprises administering a therapeutically effective amount of an anti-HIV-1 drug therapy in association with pegylated interferon-alfa.

10 48. The method of claim 47, wherein the an anti-HIV-1 drug therapy is HAART.

49. The method of claim 47, wherein the pediatric patients are treatment-naive patients.

15

50. The method of claim 47, wherein the pediatric patients are treatment-experienced patients.

52. The method of claim 47, wherein the pegylated interferon-alfa
20 administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.

53. The method of claim 47, wherein the pegylated interferon-alfa
25 administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram QW.

54. The method of claim 47, wherein the pegylated interferon-alfa
30 administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.5 to about 4.5 micrograms per kilogram QW.

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55. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 2.25 to about 2.6 micrograms per kilogram QW.

5

56. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 50 to about 500 micrograms QW.

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57. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a administered is in the range of about 300 to about 375 micrograms QW.

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58. The method of claim 47, wherein the pediatric patient is co-infected with HCV.

59. The method of claim 58, wherein ribavirin is administered to the pediatric patient in association the pegylated interferon-alfa and the amount of ribavirin is in a range of about 8 to about 15 mg per kilogram per day, in divided doses.

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60. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b administered is in the range of about 0.1 to about 9.0 micrograms per kilogram BIW

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61. The method of claim 47, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the amount of

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69. The method of claim 47, wherein a human growth is administered.
in association with

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ABSTRACT OF THE DISCLOSURE

Methods for treating treatment-naive as well as treatment-experienced adult and pediatric patients having HIV-1 infections as well as

5 patients co-infected with HIV-1 and HCV involving administering a therapeutically effective amount of pegylated interferon-alfa, e.g. , pegylated interferon alfa-2b as monotherapy or preferably in association with a therapeutically effective amount of at least one of ribavirin, IL-2, IL-

10 amount of an anti-HIV-1 drug therapy, e.g., HAART are disclosed.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	IN01003K2
	First Named Inventor	LAUGHLIN, et al
	COMPLETE IF KNOWN	
	Application Number	/
	Filing Date	December 3, 1999
	Group Art Unit	To Be Assigned
☒ Declaration Submitted with Initial Filing	OR	☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)
Examiner Name		To Be Assigned

As a below named inventor, I hereby declare that:

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

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

HIV THERAPY

the specification of which

(Title of the invention)

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY)

as United States Application Number or PCT International

Application Number and was amended on (MM/DD/YYYY) (if applicable).

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

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
			☐	YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

[Page 1 of 2]

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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

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ANTECEDENTES DE LA INVENCION

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terapéuticamente efectiva de interferón alfa pegilado suficiente para reducir los niveles detectables de HIV-1-ARN en esos pacientes.

El interferón pegilado preferido es el interferón alfa-2b pegilado, que puede ser administrado en combinación con una cantidad terapéuticamente efectiva de por lo menos uno entre ribavirina, IL-2, IL-12 y pentafusida solo o en combinación con una cantidad terapéuticamente efectiva de un fármaco para la terapia anti HIV-1.

La presente invención también presenta el uso de una farmacoterapia contra el HIV-1 e interferón alfa pegilado para la preparación de un medicamento para el tratamiento de infecciones por HIV-1 en pacientes.

La presente invención presenta además el uso de una farmacoterapia contra el HIV-1 e interferón alfa pegilado para la preparación de un medicamento para el tratamiento de infecciones por HIV-1 en pacientes, que comprende una cantidad terapéuticamente efectiva de interferón alfa pegilado y una cantidad terapéuticamente efectiva de un fármaco terapéutico anti-HIV-1 suficiente para reducir los niveles detectables de HIV-1-ARN en esos pacientes.

La farmacoterapia anti HIV-1 preferida es HAART.

En las realizaciones preferidas, la presente invención también presenta el tratamiento de pacientes con infecciones por HIV-1 en dos períodos de tiempo de tratamiento (1) un primer período de tiempo de tratamiento de aproximadamente dos a aproximadamente cuatro semanas, en el que se administra de aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado o aproximadamente 50 a aproximadamente 500 microgramos de interferón alfa-2b pegilado en una sola dosis semanal o en dosis divididas dos veces por semana, seguido por (2) un segundo período de tratamiento suficiente para reducir los niveles detectables

de HIV-1-ARN, en el que se administra una cantidad terapéuticamente efectiva de una terapia anti-HIV-1, por ejemplo HAART, asociada con aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado o aproximadamente 50 a aproximadamente 500 microgramos de interferón alfa-2b pegilado en una sola dosis semanal o en dosis divididas dos veces por semana.

La presente invención se refiere asimismo a la preparación de medicamentos para el tratamiento de pacientes por primera vez así como pacientes adultos y pediátricos con infecciones por HIV-1 que ya han experimentado tratamiento, así como los pacientes coinfectados con HIV-1 y HCV.

DESCRIPCIÓN DETALLADA

La presente invención se refiere a la preparación de medicamentos para el tratamiento de pacientes con infecciones por HIV-1, donde el tratamiento comprende una cantidad terapéuticamente efectiva de interferón alfa pegilado como monoterapia o en combinación con una cantidad terapéuticamente efectiva de por lo menos uno de ribavirina, interleucina 2 ("IL-2"), interleucina 12 ("IL-12") y pentafusida solo o en combinación con una terapia antiHIV-1, especialmente HAART, de acuerdo con la buena práctica clínica a fin de minimizar los niveles plasmáticos de NIV-1-ARN detectable. Ver, por ejemplo, A-M. Vandamme y otros en Antiviral Chemistry & Chemotherapy, 9: 187 – 203 (1998) y "Drugs for HIV Infection" en The Medical Letter Vol 39 (emisión 1015) 5 de diciembre de 1997, páginas 111 – 116. La iniciación del HAART puede tener lugar antes, después o simultáneamente con la administración de una cantidad terapéuticamente efectiva de interferón alfa pegilado de acuerdo con la presente invención. En una realización de la presente invención, el método de tratamiento de pacientes con infecciones por HIV-1 comprende dos periodos

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de tratamiento. En el primer período de tratamiento, se administra una cantidad terapéuticamente efectiva de interferón alfa durante un primer período de tiempo de tratamiento suficiente para reducir los niveles plasmáticos de HIV-1-ARN detectable en $\geq 0,5 \log_{10}$, es decir $\geq 5 \times 10^1$ preferentemente en por lo menos $0,65 \log_{10}$, es decir $\geq 0,65 \times 10^1$, más preferentemente en por lo menos un $\log_{10}$, es decir $\geq 1 \times 10^1$, muy preferentemente en por lo menos dos $\log_{10}$, es decir $\geq 2 \times 10^1$, con respecto al nivel inicial de HIV-1-ARN en plasma. En el segundo período de tratamiento, el método conlleva continuar la administración de una cantidad terapéuticamente efectiva de interferón alfa pegilado en combinación con una cantidad terapéuticamente efectiva de HAART de acuerdo con el buen criterio médico para reducir al mínimo los niveles plasmáticos de HIV-1-ARN detectable.

El término "terapia antiHIV-1" utilizado en la presente se refiere a terapias con fármacos múltiples utilizadas en los tratamientos clínicos actuales de las infecciones por HIV-1, incluyendo, aunque sin limitarse a las terapias de fármacos múltiples, por ejemplo las terapias de tres y cuatro fármacos como las descritas por A-M. Vandamme y otros en Antiviral Chemistry & Chemotherapy, 9: 187 – 203 (1998), que describe los tratamientos clínicos de infecciones por HIV-1 en la actualidad, incluso cuándo comenzar una terapia con múltiples fármacos y qué fármacos combinar. El triple farmacoterapia puede incluir dos inhibidores nucleosídicos y nucleotídicos de la transcriptasa inversa ("NRTI") y un inhibidor de la proteasa ("PI"), aunque existen numerosos factores a considerar en la elección de la HAART específica para cada paciente. Ver, por ejemplo, las Tablas 1 & 2 y la Figura 2 de "Drugs for HIV Infección" de A-M. Vandamme y otros, citada anteriormente.

El término "pacientes con infecciones por HIV-1" utilizado en la presente se refiere a cualquier paciente – incluso un paciente pediátrico – que padece

una infección por HIV-1 e incluye a pacientes que no han recibido tratamiento y a pacientes que han experimentado tratamientos que tienen la infección por HIV-1, así como pacientes que no han recibido tratamientos anteriores y pacientes que han experimentado tratamientos coinfectados con el virus HIV-1 y el de la hepatitis C ("HCV").

En la presente, el término "paciente pediátrico" utilizado en la presente se refiere a un paciente que tiene menos de 17 años de edad y normalmente incluye a los pacientes desde el nacimiento hasta los 16 años de edad.

El término "pacientes que no han recibido tratamiento" utilizado en la presente se refiere a pacientes que tienen HIV-1 o están coinfectados con el HIV-1 y el HCV que nunca han sido tratados con fármacos antirretrovirales, por ejemplo NRTI, NNRTI, PI ni ningún interferón, incluyendo, aunque sin limitarse al interferón alfa o al interferón alfa pegilado.

El término "pacientes que han experimentado tratamientos" se utiliza en la presente para distinguir a aquellos pacientes que tienen HIV-1 o están coinfectados con el HIV-1 y el HCV, que han iniciado alguna forma de terapia antiHIV incluyendo, aunque sin limitarse a HAART o alguna forma de terapia anti-HCV, incluyendo, aunque sin limitarse a interferón alfa, interferón alfa pegilado o ribavirina.

El término "pacientes con infecciones por hepatitis C" se utiliza en la presente para indicar a cualquier paciente – incluso un paciente pediátrico – que tiene hepatitis C e incluye pacientes que nunca han recibido tratamiento y pacientes que han experimentado tratamientos, con infecciones por hepatitis C así como los pacientes pediátricos, que no han recibido tratamiento y con experiencia en tratamientos con infecciones por hepatitis C crónicas.

Entre estos pacientes con hepatitis C se cuentan aquéllos que están infectados con múltiples genotipos de HCV, incluyendo el tipo 1, así como los

infectados, por ejemplo, con los genotipos de HCV 2, 3, 4, 5 y/o 6 y otros genotipos de posibles HCV posibles.

El término "pacientes con infecciones por hepatitis C que no han recibido tratamiento" se utiliza en la presente para indicar pacientes con hepatitis C que nunca han sido tratados con ribavirina ni con algún interferón, incluyendo, aunque sin limitarse a interferón alfa o interferón alfa pegilado.

El término "pacientes con infecciones por hepatitis C que han experimentado tratamientos (con experiencia en tratamientos)" utilizado en la presente se refiere a pacientes con hepatitis C que han sido tratados con ribavirina o con algún interferón, incluyendo, aunque sin limitarse a interferón alfa o interferón alfa pegilado, incluso los que sufren recaídas y los que no responden.

El término "que sufren recaídas" utilizado en la presente se refiere a pacientes con hepatitis C que han experimentado tratamientos y que han sufrido recaídas tras la respuesta inicial a un tratamiento anterior con interferón solo o en combinación con ribavirina.

El término "que no responden" utilizado en la presente se refiere a pacientes con hepatitis C que han experimentado tratamientos y que no han respondido al tratamiento anterior con ningún interferón solo ni en combinación con ribavirina.

Cuando el interferón alfa pegilado administrado es un interferón alfa-2b pegilado, la cantidad terapéuticamente efectiva de interferón alfa-2b pegilado administrada durante el tratamiento de acuerdo con la presente invención, incluyendo el primer y segundo períodos de tratamiento, está en el rango de aproximadamente 0,1 a 9,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado por semana, en una sola dosis o en dosis divididas, preferentemente una vez por semana (QW) o dos veces por semana (BIW),

infectados, por ejemplo, con los genotipos de HCV 2, 3, 4, 5 y/o 6 y otros genotipos de posibles HCV posibles.

El término "pacientes con infecciones por hepatitis C que no han recibido tratamiento" se utiliza en la presente para indicar pacientes con hepatitis C que nunca han sido tratados con ribavirina ni con algún interferón, incluyendo, aunque sin limitarse a interferón alfa o interferón alfa pegilado.

El término "pacientes con infecciones por hepatitis C que han experimentado tratamientos (con experiencia en tratamientos)" utilizado en la presente se refiere a pacientes con hepatitis C que han sido tratados con ribavirina o con algún interferón, incluyendo, aunque sin limitarse a interferón alfa o interferón alfa pegilado, incluso los que sufren recaídas y los que no responden.

El término "que sufren recaídas" utilizado en la presente se refiere a pacientes con hepatitis C que han experimentado tratamientos y que han sufrido recaídas tras la respuesta inicial a un tratamiento anterior con interferón solo o en combinación con ribavirina.

El término "que no responden" utilizado en la presente se refiere a pacientes con hepatitis C que han experimentado tratamientos y que no han respondido al tratamiento anterior con ningún interferón solo ni en combinación con ribavirina.

Cuando el interferón alfa pegilado administrado es un interferón alfa-2b pegilado, la cantidad terapéuticamente efectiva de interferón alfa-2b pegilado administrada durante el tratamiento de acuerdo con la presente invención, incluyendo el primer y segundo periodos de tratamiento, está en el rango de aproximadamente 0,1 a 9,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado por semana, en una sola dosis o en dosis divididas, preferentemente una vez por semana (QW) o dos veces por semana (BIW),

preferentemente en el rango de 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana (QW), en el rango de aproximadamente 0,05 a aproximadamente 4,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana, o está en el rango de aproximadamente 0,5 a aproximadamente 3,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana, preferentemente en el rango de aproximadamente 0,5 a aproximadamente 3,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana (QW) o en el rango de aproximadamente 0,25 a aproximadamente 1,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana, o está en el rango de aproximadamente 0,75 a aproximadamente 1,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado por semana, muy preferentemente en el rango de aproximadamente 0,75 a aproximadamente 1,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana o de aproximadamente 0,375 a aproximadamente 0,75 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana.

Cuando el interferón alfa pegilado administrado a pacientes pediátricos es un interferón alfa 2-b pegilado, la cantidad terapéuticamente efectiva de interferón alfa-2b pegilado administrado durante el tratamiento de acuerdo con la presente invención, incluso en el primer y segundo periodos de tratamiento, está en el rango de 0,1 a 9,0 microgramos por kilogramo de interferón alfa-2b pegilado por kilogramo de interferón alfa-2b pegilado administrado por semana, en una sola dosis o en dosis divididas, preferentemente una vez por semana (QW) o dos veces por semana (BIW), más preferentemente de 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado

administrado una vez por semana (QW), o aproximadamente 0,05 a aproximadamente 4,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado por semana, en dosis únicas o divididas, preferentemente una vez por semana (QW) o dos veces por semana (BIW), más preferentemente de aproximadamente 0,05 a 4,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana, preferentemente de aproximadamente 0,75 a aproximadamente 3,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado en dosis únicas o divididas, preferentemente una vez por semana (QW) o dos veces por semana (BIW), más preferentemente de aproximadamente 0,75 a aproximadamente 3,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana o de aproximadamente 0,375 a aproximadamente 1,5 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana, y muy preferentemente de aproximadamente 2,25 a aproximadamente 2,6 microgramos por kilogramo de interferón alfa-2b pegilado administrado una vez por semana o aproximadamente 1,125 a aproximadamente 1,3 microgramos por kilogramo de interferón alfa-2b pegilado administrado dos veces por semana (BIW). En una realización preferida de la presente invención, se administran dosis pediátricas de aproximadamente 0,75 a aproximadamente 3,0 microgramos por kilogramo de interferón alfa-2b pegilado una vez por semana.

Cuando el interferón alfa pegilado administrado es un interferón alfa-2b pegilado, la cantidad terapéuticamente efectiva de interferón alfa-2b pegilado administrada durante el tratamiento de acuerdo con la presente invención, incluyendo el primer y segundo periodos de tratamiento, está en el rango de aproximadamente 50 microgramos a aproximadamente 500 microgramos una vez por semana ("QW"), preferentemente de aproximadamente 200 a

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aproximadamente 250 microgramos QW o la cantidad efectiva está en el rango de aproximadamente 50 microgramos a aproximadamente 250 microgramos dos veces por semana, preferentemente de aproximadamente 100 microgramos a aproximadamente 125 microgramos dos veces por semana.

Cuando el interferón alfa pegilado administrado a un paciente pediátrico es un interferón alfa 2-b pegilado, la cantidad terapéuticamente efectiva de interferón alfa-2b pegilado administrado durante el tratamiento de acuerdo con la presente invención, incluso en el primer y segundo periodos de tratamiento, está en el rango de aproximadamente 50 microgramos a aproximadamente 500 microgramos una vez por semana ("QW"), preferentemente de aproximadamente 300 a aproximadamente 375 microgramos QW o la cantidad efectiva administrada a un paciente pediátrico está en el rango de aproximadamente 50 microgramos a aproximadamente 250 microgramos dos veces por semana, preferentemente de aproximadamente 150 microgramos a aproximadamente 190 microgramos una vez por semana.

La ribavirina se administra al paciente en combinación con el interferón alfa pegilado; es decir, antes, después o simultáneamente con la administración del interferón alfa pegilado. La dosis de interferón alfa pegilado se administra preferentemente durante el mismo periodo de tiempo en que el paciente recibe dosis de ribavirina. La cantidad de ribavirina administrada simultáneamente con el interferón alfa pegilado es de aproximadamente 400 a aproximadamente 1600 mg por día, preferentemente de aproximadamente 600 a aproximadamente 1200 mg/día o de aproximadamente 800 a aproximadamente 1200 mg por día y, muy preferentemente, de aproximadamente 1000 a aproximadamente 1200 mg/kg por día. En el paciente pediátrico, la dosis de interferón alfa pegilado también se administra durante el mismo periodo de tiempo en que dicho paciente recibe dosis de ribavirina. La

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08543, lamivudina (3TC) comercializada bajo la denominación comercial EPIVIR de Glaxo-Wellcome Inc., Research Triangle, NC 27709; abacavir (1592U89) descrita en WO 96/30025 comercializada bajo la denominación comercial ZIAGEN de Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] comercializada bajo la denominación comercial PREVON de Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194) un inhibidor nucleosídico de la transcriptasa inversa descrito en EP-0358154 y EP-0736533 y en desarrollo por Bristol-Myers Squibb, Princeton, NNJ 08543; BCH-10652, un inhibidor de la transcriptasa inversa (en forma de mezcla racémica de BCH-10618 y BCH-10619) en desarrollo por Biochem Pharma, Laval, Québec H7V, A47, Canadá; emitricitabina [(-)-FTC] con licencia de Emory University bajo la patente de los Estados Unidos No. 5.814.639 y en desarrollo por Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4 (también denominado beta-L-D4C y beta-L-2',3'-dicleoxi-5-fluorocitideno), con licencia de la Universidad de Yale concedida a Vion Pharmaceuticals, New Haven CT 06511 y DAPD, el nucleósido de purina, (-)-beta-D-2,6-diaminopurina dioxolano descrito en EP 0656778 y otorgado por licencia de la Universidad Emory y la Universidad de Georgia a Triangle Pharmaceuticals, Durham, NC 27707; y Iodenosina (FDA), 9-(2,3-dideoxi-2-fluoro-b-D-treo-pentofuranosil)adenina, un inhibidor de la transcriptasa inversa a base de purina estable en ácido descubierto por el NIH y en desarrollo por U.S. Bioscience Inc., Conshohocken Oeste, PA. 19428.

El término "inhibidores no nucleosídicos de la transcriptasa inversa ("NNRTI"s) utilizado en la presente significa no nucleósidos que inhiben la actividad de la transcriptasa inversa del HIV-1.

Los inhibidores no nucleosídicos de la transcriptasa inversa típicos adecuados incluyen nevirapina (BI-RG-587), comercializado bajo la

denominación comercial VIRAMUNE de Boehringer Ingelheim, el fabricante para Roxane Laboratories, Columbus, OH 43216; delaviradina (BHAP, U-90152) comercializado bajo la denominación comercial RESCRIPTOR de Pharmacia & Upjohn Co. Bridgewater NJ 08807; efavirenz (DMP-266) una benzoxazin-2-ona descrita en WO 94/03440 y comercializada bajo la denominación comercial SUSTIVA de DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, una furopiridina-tiopirimida en desarrollo por Pharmacia & Upjohn Co. Bridgewater NJ 08807; AG-1549 (antes Shionogi # S-1153); carbonato de 5-(3,5-diclorofenil)-tio-4-isopropil-1-(4-piridil)metil-1H-imidazol-2-ilmetilo descrito en WO 96/ 10019 y en desarrollo clínico por Agouron Pharmaceuticals, Inc., La Jolla, CA 92037-1020; 1-(etoximetil)-5-(1-metiletil)-6-(fenilmetil)-(2,4(1H,3H)-pirimidinadiona MKC-442 descubierta por Mitsubishi Chemical Co. y en desarrollo por Triangle Pharmaceuticals, Durham, NC 27707 y derivados de (+)-calanolida A (NSC-675451) y cumarina B descritos en La patente de los Estados Unidos No. 5.489.697 del NIH, con licencia otorgada a Med Chem Research, que está codesarrollando la (+) calanolida A con Vita-Invest como producto para la administración oral.

El término "inhibidor de la proteasa" ("PI") utilizado en la presente se refiere a inhibidores de la proteasa del HIV-1, una enzima necesaria para la escisión proteolítica de los precursores de poliproteínas virales (por ejemplo, las poliproteínas virales GAG y GAG Pol) para la obtención de proteínas funcionales individuales encontradas en el HIV-1 infeccioso. Los inhibidores de la proteasa del HIV incluyen compuestos con estructura peptidomimética, alto peso molecular (7600 daltons) y carácter peptídico considerable, por ejemplo CRIXIVAN (comercializado por Merck), así como inhibidores de la proteasa no peptídicos, por ejemplo VIRACEPT (comercializado por Agouron).

Entre los inhibidores de la proteasa típicos adecuados se incluyen el saquinavir (Ro 31-8959) comercializado en cápsulas de gelatina dura bajo la denominación comercial INVIRASE y en forma de cápsulas de gelatina blanda bajo la denominación comercial FORTOUASE de Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) comercializado bajo la denominación comercial NORVIR de Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) comercializado bajo la denominación comercial CRIVAN DE Merck & Co., Inc., West Point PA 19486-0004; nelfinavir (AG-1343) comercializado bajo la denominación comercial VIRACEPT por Agouron Pharmaceuticals, Inc., La Jolla, CA 92037-1020; amprenavir (141W94) un inhibidor no peptídico de la proteasa en desarrollo por Vertex Pharmaceuticals, Inc. Cambridge, MA 02139-4211 y comercializado por Glaxo-Wellcome, Research Triangle, NC según un programa de acceso expandido; lasinavir (BMS-234475) comercializado por Bristol-Myers Squibb Co., Princeton, NJ 08543, originariamente descubierto por Novartis, Basilea, Suiza (CGP-61755); DMP-450, una urea cíclica descubierta por Dupont y en desarrollo por Triangle Pharmaceuticals; BMS-2322623, un azapéptido en desarrollo por Bristol-Myers Squibb Co., Princeton, NJ 08543, como PI del HIV-1 de 2a. generación y ABT-378 en desarrollo por Abbott, Abbott Park, IL 60064 y AG-1549, un carbamato de imidazol con actividad oral descubierta por Shionogi (Shionogi #S-1153) y en desarrollo por Agouron Pharmaceuticals, Inc., La Jolla, CA 92037-1020.

El término "terapia anti HIV-1" utilizado en la presente significa cualquier fármaco anti-HIV-1 considerado de utilidad para el tratamiento de infecciones por HIV-1 en el hombre solo o como parte de terapias de combinación de múltiples fármacos, especialmente las terapias de triple y cuádruple combinación denominadas HAART.

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Las terapias anti-HIV-1 típicas adecuadas incluyen, aunque no se limitan a terapias de combinación de múltiples fármacos tales como (i) por lo menos tres drogas anti-HIV-1 seleccionadas entre dos NRTI, un PI, un segundo PI y un NNRTI; y (ii) por lo menos dos drogas anti-HIV-1 seleccionadas entre NNRTI y PI; ver Tablas I, II y III más adelante.

Las HAART - terapias combinatorias de fármacos múltiples - típicas adecuadas incluyen (a) terapias de triple combinación tales como dos NRTI y un PI o (b) dos NRTI y un NNRTI y (c) terapias de cuádruple combinación tales como dos NRTI, un PI y un segundo PI o un NNRTI. En pacientes que no han recibido tratamientos anteriores, se prefiere el uso de dos NRTI y un PI a menos que exista una intolerancia a los PI. Es esencial el cumplimiento con la droga. Los niveles plasmáticos de CD4⁺ y HIV-1-ARN deben ser monitoreados cada 3 – 6 meses. si la carga viral se estacionara, se podría agregar una cuarta droga, por ejemplo un PI y un NNRTI. Ver la Tabla A presentada a continuación.

Tabla A

TERAPIAS COMBINATORIAS DE FÁRMACOS MÚLTIPLES ANTI-HIV-

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A. Terapias combinatorias triples

1. Dos NRTI¹ + un PI²

2. Dos NRTI¹ + un NNRTI³

B. Terapias combinatorias cuádruples⁴

Dos NRTI + un PI + un segundo PI o un NNRTI

C. ALTERNATIVAS⁵

Dos NTRI¹

Un NTRI⁵ + un PI²

Dos PI⁶ + un NTRI⁷ o NNRTI³

Un PI² + un NRTI⁷ + un NNRTI³

Notas al pie de la Tabla A

1. Una de las siguientes: zidovudina + lamivudina; zidovudina + didanosina; stavudina + lamivudina; stavudina + didanosina; zidovudina + zalcitabina; Ver también la Tabla I

2. Indinavir, nelfinavir, ritonavir o saquinavir cápsulas de gelatina blanda.

El ritonavir se utiliza con menos frecuencia a raíz de sus efectos adversos problemáticos. La vieja formulación de saquinavir se utilizaba con menos frecuencia en virtud de su baja biodisponibilidad y limitada efectividad, aunque la nueva formulación de saquinavir debería ser más eficaz. Ver también la Tabla III.

3. Nevirapina o delavirdina. Ver también la Tabla II.

4. Ver A-M. Vandamme y otros, Antiviral Chemistry + Chemotherapy 9: 187 en la pág. 193 – 197 y las Figuras 1 + 2.

5. Los regímenes alternativos son para pacientes que no pueden tomar un régimen recomendado por problemas de observancia o toxicidad y para quienes fracasan o sufren una recaída con el régimen recomendado. Las combinaciones dobles de nucleósidos pueden llevar a la resistencia al HIV y a la falla clínica en muchos pacientes.

6. La mayoría de los datos obtenidos corresponden a saquinavir y ritonavir (cada puesta de 400 mg). Ver también la Tabla III.

7. Zidovudina, stavudina o didanosina. Ver también la Tabla I.

Otras drogas contra el HIV-1 que sirven para ser administradas en combinación con el interferón alfa pegilado incluyen la hidroxiurea, ribavirina, IL-2 e IL-12, así como el Proyecto Yisum No. 11607. Estas drogas anti-HIV-1 citadas también se pueden administrar en combinación con interferón alfa pegilado combinado con cualquier farmacoterapia contra el HIV-1,

especialmente las combinaciones triples y cuádruples de fármacos denominadas HAART.

La hidroxiurea (Droxia) es un inhibidor de la ribonucleósido trifosfato reductasa, la enzima implicada en la activación de las células T. La hidroxiurea descubierta en el NCI está en desarrollo por Bristol-Myers Squibb. En los estudios preclínicos, se demostró que tiene efecto sinérgico sobre la actividad de la didanosina y ha sido estudiada con stavudina.

Proyecto Yisum No. 11607, una proteína sintética basada en la proteína Vif del HIV-1 en desarrollo preclínico por Yisum Research Development Co., Jerusalem 91042, Israel.

El interferón alfa pegilado, PEG₁₂₀₀₀-IFN-alfa2b (comercializado por Schering-Plough Research Institute, Kenilworth, NJ) aumentó la actividad de la ribavirina in vitro contra el HIV-1. La combinación de PEG₁₂₀₀₀-IFN-alfa2b y ribavirina inhibió la replicación del HIV in vitro utilizando células mononucleares de sangre periférica ("PBMC") activadas con fitohemaglutinina ("PHA"-P) en dosis correspondientes a las concentraciones plasmáticas observadas en animales y en el hombre. Se separaron las PBMC sanas de una capa decapada de un donante de sangre HIV seronegativo por centrifugación en gradiente de densidad con Ficoll-Hypaque. Las PBMC fueron activadas con 1 µg/ ml de fitohemaglutinina (PHA-P) durante dos días en un medio de cultivo celular A: RPMI 1640 suplementado con plasma fetal bovino (FCS) termoinactivado al 10 % (+56°C, 45 min.), 2 mM de L-glutamina y una mezcla de tres antibióticos (penicilina, estreptomicina, neomicina; PSN). Al cabo de estos dos días, las células fueron lavadas y cultivadas a razón de un millón de células por mililitro en medio de cultivo celular B: medio de cultivo celular A suplementado con 20 UI/ ml de interleucina 2 recombinante humana. Se mantuvo a las células a +37°C en atmósfera humectada con CO₂ 5 %- aire. Los

experimentos fueron repetidos dos veces con células de otros donantes de sangre. En total, se realizaron tres experimentos independientes.

Se infectó a las PBMC con 1000 Dosis Infecciosas al 50 % del Cultivo Tisular (TCID₅₀) de la cepa HIV-1-LAI de referencia [F. Barre-Sinoussi, Science, 1983, 220, 868 – 871]. Esta cepa ha sido amplificada empleando células mononucleares de sangre umbilical activadas con PHA-P (UBMC). Luego se tituló la base de cultivo viral con PBMC activadas con PHA-P mediante dilución al punto final. Luego se calculó la TCID₅₀ utilizando la fórmula de Karber [Arch. Exp. Path. Pharmacol., 1931, 162, 126 – 133].

Se administró el PEG₁₂₀₀₀-IFN- α 2b y la ribavirina, solos y en combinación, así como el AZT utilizado como control, 24 horas antes de la infección con HIV-1 y se mantuvieron durante todo el cultivo. Se utilizaron tres dosis de PEG₁₂₀₀₀-IFN- α 2b y ribavirina.

Se agregaron 200.000 PBMC activadas con PHA-P en cada receptáculo de las microplacas de 96 receptáculos. Las células fueron sometidas a tratamiento previo 24 horas antes de la infección con la cepa HIV-1-LAI de referencia. Dos veces por semana se recogían los sobrenadantes celulares y se renovaban los fármacos y el medio. En el día 7, se determinó la actividad de TI en los sobrenadantes celulares y se evaluaron los potenciales efectos citotóxicos de las drogas y las combinaciones de drogas mediante observación microscópica.

Se midió la replicación viral determinando la actividad de transcriptasa inversa ("TI") en los sobrenadantes celulares utilizando el kit de la denominación comercial Retro-Sys de acuerdo con las recomendaciones del fabricante (Innovagen, Lund, Suecia).

Se calcularon las dosis efectivas utilizando actividades acumulativas de TI con el software de microcomputadora de J. y TC Chou.

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Se analizaron los efectos combinados utilizando el índice de combinación (IC) [Chou & Talalay, 1984] con el software de microcomputadora de J. y TC Chou, o bien el índice de concentración inhibitoria fraccionada (CIF) [Antimicrob. Agents. Chemother., 1987, 31, 1613 – 1617]. Cuando el índice IC o CIF es igual a 1, la combinación es aditiva. Cuando es inferior a 1,0, la combinación es sinérgica y, cuando es superior a 1,0, se considera que la combinación es antagonista.

El PEG₁₂₀₀₀-IFN- α 2b, así como la combinación de PEG₁₂₀₀₀-IFN- α 2b y ribavirina y la ribavirina inhibieron la replicación en dosis correspondientes a las concentraciones plasmáticas determinadas en ratones y pacientes infectados con HIV-1 [BE. Gilbert y otros, Antimicrob. Agents. Chemother., 1988, 32, 117 – 121; E. Connor y otros, Antimicrob. Agents. Chemother., 1993, 37, 537 – 539].

La IL-2 ha sido descrita en EP-0142268 de Ajinomoto, EP-0176299 de Takeda y las patentes de los Estados Unidos Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585 y 4949314 de Chiron, y es comercializada por Chiron Corp., Emeryville, CA 94608-2997 bajo la denominación comercial PROLEUKIN (aldesleukin) en forma de polvo liofilizado para infusión IV o administración sc tras la reconstitución y dilución con agua; son preferibles dosis de aproximadamente 1 a aproximadamente 20 millones de UI/ día; es más preferible una dosis de alrededor de 15 millones de UI/ día por vía sc.

La IL-12 ha sido descrita en WO 96/25171 y es comercializada por Roche Pharmaceuticals, Nutley, NJ 01770-1199 y American Home Products, Madison, NJ 07940, prefiriéndose una dosis de aproximadamente 0,5 microgramos/ kg/ día a aproximadamente 10 microgramos/ kg/ día por vía sc.

La pentafusida (DP-178, T-20) es un péptido de 36 aminoácidos, descrito en la patente de los Estados Unidos No. 5.464.933 con licencia de

Duke University a Trimeris, que está desarrollando la pentafusida en colaboración con la universidad de Duke. La pentafusida actúa inhibiendo la fusión del HIV-1 con las membranas target. La pentafusida (3 – 100 mg/día) se da en infusión continua o inyección sc junto con efavirenz y 2 PI a los pacientes HIV-positivos refractarios a la terapia de combinación triple; se prefiere el uso de 100 mg/día.

El término "interferón alfa" utilizado en la presente se refiere a la familia de proteínas de especies específicas altamente homólogas que inhiben la replicación viral y la proliferación celular y modulan la respuesta inmune. Los interferones alfa típicos adecuados incluyen, aunque no se limitan a, interferón alfa-2b recombinante tal como el interferón Intron-A comercializado por Schering Corporation, Kenilworth, N.J., el interferón alfa-2b recombinante, por ejemplo el interferón Roferon comercializado por Hoffmann-La Roche, Nutley, N.J., el interferón alfa-2C recombinante como el interferón alfa 2 Berofor comercializado por Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferón alfa-n1, una mezcla purificada de interferones alfa naturales tales como Sumiferon, comercializado por Sumitomo, Japón o como interferón alfa-n1 Wellferon (INS) comercializado por Glaxo-Wellcome Ltd., Londres, Gran Bretaña, o un interferón alfa consenso tal como el descrito en las patentes de los Estados Unidos Nos. 4.897.471 y 4.695.623 (especialmente los Ejemplos 7, 8 ó 9 de las mismas) y el producto específico comercializado por Amgen, Inc., Newbury Park, CA, o interferón alfa-n3, una mezcla de interferones alfa naturales elaborada por Interferon Sciences y comercializada por la Purdue Frederick Co., Norwalk, CT, bajo la denominación comercial Alferón. Se prefiere el uso de interferón alfa-2a o alfa 2b. Dado que el interferón alfa 2b, entre todos los interferones, goza de la más amplia aprobación en todo el mundo para el tratamiento de la infección crónica por hepatitis C, es el más

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preferido. La elaboración del interferón alfa 2b ha sido descripta en la patente de los Estados Unidos No. 4.530.901.

El término "interferón alfa pegilado" utilizado en la presente significa conjugados de interferón alfa, preferentemente interferón alfa-2a y -2b, modificados con polietilenglicol. El conjugado polietilenglicol- interferón alfa-2b preferido es el PEG₁₂₀₀₀- interferón alfa 2b. Las frases "interferón alfa conjugado con polietilenglicol de peso molecular 12000" y "PEG₁₂₀₀₀-IFN alfa" utilizadas en la presente se refieren a conjugados tales como los preparados de acuerdo con los métodos de la Solicitud internacional No. WO 95/13090 y que contiene ligamientos de uretano entre los grupos interferón alfa-2a o -2b y polietilenglicol con un peso molecular medio de 12000.

El PEG₁₂₀₀₀-interferón alfa-2b preferido se prepara uniendo un polímero de PEG al grupo amino epsilon de un residuo de lisina en la molécula de IFN alfa-2b. Se conjuga una sola molécula de PEG₁₂₀₀₀ a los grupos amino libres de una molécula de IFN alfa-2b por medio de un ligamiento de uretano. Este conjugado se caracteriza por el peso molecular del PEG₁₂₀₀₀ fijado. El conjugado PEG₁₂₀₀₀-IFN alfa-2b se formula en forma de polvo liofilizado para inyección. El objetivo de la conjugación del IFN alfa con el PEG es mejorar la administración de la proteína prolongando significativamente su vida media en plasma y, de esa manera, producir una actividad prolongada del IFN alfa.

Se pueden preparar otros conjugados de interferón alfa acoplando un interferón alfa a un polímero hidrosoluble. Una lista no limitante de dichos polímeros incluyen otros homopolímeros de óxido de polialquileno tales como glicoles de polipropileno, polioles polioxietilenados, copolímeros de los mismos y copolímeros en bloque de los mismos. Como alternativa a los polímeros a base de óxido de polialquileno, se pueden utilizar materiales efectivamente no antigénicos tales como el dextrano, las polivinilpirrolidonas, poliacrilamidas,

alcoholes polivinílicos, polímeros a base de carbohidratos y demás. Tales conjugados de interferón alfa – polímero han sido descritos en la patente de los Estados Unidos No. 4.766.106, la patente de los Estados Unidos No. 4.917.888, la solicitud de patente europea No. 0 236 987, las solicitudes de patente europea Nos. 0510 356, 0 593 868 y 0 809 996 (interferón alfa-2a pegilado) y la publicación internacional No. WO 95/13090.

La composición farmacéutica de interferón alfa pegilado adecuada para la administración parenteral puede ser formulada con un buffer adecuado, por ejemplo Tris-HCl, acetato o fosfato, por ejemplo buffer de fosfato de sodio dibásico/ fosfato de sodio monobásico y excipientes farmacéuticamente aceptables (por ejemplo, sacarosa), vehículos (por ejemplo, albúmina plasmática humana), agente de toxicidad (por ejemplo NaCl), conservantes (por ejemplo NaCl), conservantes (por ejemplo timerosal, cresol o benilalcohol) y tensioactivos (por ejemplo tween. o polisorbatos) en agua estéril para inyección. El interferón alfa pegilado puede ser almacenado en forma de polvos liofilizados con refrigeración a 2° - 8°C. Las soluciones acuosas reconstituidas son estables en almacenamiento a entre 2° y 8°C y utilizados dentro de las 24 horas de su reconstitución. Ver, por ejemplo, las patentes de los Estados Unidos Nos. 4.492.537; 5.762.923 y 5.766.582. Las soluciones acuosas reconstituidas también pueden ser almacenadas en jeringas precargadas con dosis múltiples tales como las que sirven para la administración de drogas tales como la insulina. Las jeringas típicas adecuadas incluyen disposiciones que comprenden un frasco precargado unido a una jeringa símil lapicera tal como NOVOLET Novo Pen comercializada por Novo Nordisk, así como jeringas lapicera recargadas que permiten la fácil autoinyección por parte del usuario. Otras disposiciones de jeringa incluyen una jeringa tipo lapicera que

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comprende un cartucho de vidrio que contiene un diluyente y polvo de interferón alfa pegilado en un compartimiento separado.

Una persona que padece una infección crónica por hepatitis C puede exhibir uno o más de los siguientes signos o síntomas:

- (a) ALT elevada
- (b) prueba positiva para anticuerpos anti HCV,
- (c) presencia de HCV demostrada por una prueba positiva para determinar la presencia de HCV-ARN en el suero,
- (d) signos clínicos de enfermedad hepática crónica,
- (e) lesión hepatocelular.

Para llevar a la práctica la invención, se administra la terapia combinatoria de interferón alfa pegilado y ribavirina en combinación con una terapia antirretroviral, por ejemplo HAART, al paciente infectado por el HIV-1 y que exhibe uno o más de los mencionados signos o síntomas en el primer y segundo período de tratamiento, en cantidades suficientes para eliminar, o por lo menos mitigar, uno o más de los signos o síntomas y para reducir los niveles de HCV-ARN en suero en por lo menos una potencia de diez, y preferentemente para erradicar el GCV-ARN detectable por lo menos hacia el final de segundo período de tratamiento y a fin de que el HCV-ARN siga siendo no detectable durante por lo menos 24 semanas posteriores al final del segundo período de tratamiento. La suma del primer y segundo períodos de tratamiento es de aproximadamente 40 – 50 semanas y preferentemente de 48 semanas. La administración de ribavirina se puede interrumpir tras el final del segundo período de tratamiento según el criterio del médico a cargo.

El término "ACV-ARN no detectable" en el contexto de la presente invención, significa que hay menos de 100 copias del HCV-ARN por ml de suero del paciente medidas por metodología de PCR de transcriptasa inversa

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cuantitativa de múltiples ciclos. El ACV-ARN se mide, preferentemente en la presente invención, por metodología RT-PCR basada en las investigaciones, muy conocida por los clínicos especializados. En la presente se hace referencia a esta metodología como HCV-ARN/qPCR. El límite mínimo de detección de HCV-ARN es de 100 copias/ml. Los análisis séricos de HCV-ARN/qPCR y las pruebas de genotipo de HCV se realizan en un laboratorio central. Ver también J. G. McHutchinson y otros (N. Engl. J. Med., 1998, 339: 1485- 1492) y G. L. Davis y otros (N. Engl. J. Med., 339: 1493 – 1499).

En una realización preferida de la presente invención, los pacientes coinfectados con HIV-1 y HCV son tratados con interferón alfa pegilado en combinación con ribavirina y una combinación HAART considerada apropiada por el médico a cargo y el paciente; se prefiere el uso de la terapia combinatoria de interferón alfa-2b y ribavirina comercializada por Schering Corp. bajo la denominación comercial REBETRON. Ver también J. G. McHutchinson y otros (N. Engl. J. Med., 1998, 339: 1485- 1492) y G. L. Davis y otros (N. Engl. J. Med., 339: 1493 – 1499). La ribavirina, 1- β -D-ribofuranosil-1H-1,2,4-triazol-3-carboxamida, comercializada por ICN Pharmaceuticals, Inc., Costa Mesa, California, está descrita en el Índice Merck, compuesto No. 8199, Undécima Edición. Su elaboración y formulación ha sido descrita en la patente de los Estados Unidos No. 4.211.771.

Para el paciente pediátrico coinfectado con infecciones por HIV-1 y HCV, una HAART adecuada incluye un NRTI + un PI, por ejemplo Nelfinavir + un NNRTI, por ejemplo Efavirenz en combinación con los dosajes y regímenes de dosaje para el interferón alfa pegilado y la ribavirina antes enumerados. Ver también las Tablas I – IV expuestas más adelante en la presente. A estos pacientes pediátricos se les puede administrar una hormona de crecimiento humana, como la hormona polipeptídica somatropina, de origen ADNr

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recombinante, comercializada bajo la denominación comercial HUMATROPE por Eli Lilly & Co., Indianápolis, IN 46285, en la dosis y régimen de administración enumerados en el prospecto del producto consultando con el clínico interviniente para reducir el retardo del crecimiento asociado con el tratamiento con interferón alfa pegilado.

La HAART se administra al paciente en combinación con el interferón alfa pegilado, es decir que la dosis de interferón alfa pegilado puede ser administrada antes, después o durante el período de tiempo en que el paciente recibe dosis de HAART. Se puede administrar al paciente pediátrico con infección por HIV-1 una hormona de crecimiento humano tal como la hormona polipeptídica somatropina, de origen ADNr recombinante, comercializada bajo la denominación comercial HUMATROPE por Eli Lilly & Co., Indianápolis, IN 46285, en la dosis y régimen de administración enumerados en el prospecto del producto de acuerdo con el clínico interviniente.

En una realización preferida, el interferón alfa pegilado se administra a pacientes infectados por HIV-1 antes de la iniciación de la HAART y, preferentemente, aproximadamente dos a aproximadamente cuatro semanas antes de la iniciación de la HAART. En otra realización preferida de la presente invención, se da comienzo a la administración del interferón alfa pegilado simultáneamente, es decir, el mismo día que se inicia la administración de HAART. En otra realización preferida de la presente invención, el interferón alfa pegilado se administra una vez que el paciente infectado por HIV-1 ha iniciado la HAART.

La meta de la terapia contra el HIV-1 de acuerdo con la presente invención es reducir la carga viral de HIV-1-ARN por debajo del límite detectable. El "límite de HIV-1-ARN detectable" significa, en el contexto de la presente invención, que hay menos de aproximadamente 200 a menos de

aproximadamente 50 copias de HIV-1-ARN por ml de plasma del paciente según determinación por metodología de PCR de transcriptasa inversa cuantitativa de múltiples ciclos. Preferentemente, en la presente invención, el HIV-ARN se mide por la metodología de Amplicor-1, Monitor 1,5 (comercializado por Roche Diagnostics) o de Nuclisens HIV-1 QT-1. Esta metodología fue descrita por Schooley, RT, Antiviral Therapy (1997), 2 (Supl. 4): 59 – 70.

Las dosis y el régimen de dosificación de los NRTI, NNRTI y PI; IL-2, IL-12 y pentafusida deben ser determinados por el médico a cargo en vista de las dosis y régimen de dosificación aprobados en el prospecto o expuestos en el protocolo tomando en cuenta la edad, el sexo y estado del paciente, así como la gravedad de la infección por HIV-1. Para el paciente pediátrico infectado con el HIV-1 o coinfectado con HIV-1 y HCV, una HAART típica incluye un NRTI + un PI, por ejemplo el Nelfinavir + un NNRTI, por ejemplo Efavirenz en combinación con los dosajes y regímenes de dosaje para el interferón alfa pegilado y la ribavirina antes enumerados. Ver también las Tablas I – IV expuestas más adelante en la presente para tomar conocimiento de los dosajes y regímenes de dosaje.

Se pueden utilizar los siguientes protocolos clínicos para administrar la terapia anti HIV-1 de la presente invención. El médico especialista considerará evidentes las numerosas modificaciones posibles de este protocolo clínico y los siguientes Diseños de Estudio no deben ser considerados limitantes del alcance del método de la presente invención, que sólo está limitado por las reivindicaciones adjuntas. Ver, por ejemplo, J. G. McHutchinson y otros (N. Engl. J. Med., 1998, 339: 1485- 1492) y G. L. Davis y otros (N. Engl. J. Med., 339: 1493 – 1499).

La población en estudio incluye pacientes de sexo masculino y femenino con diagnóstico de infección por HIV-1 que no han recibido tratamiento anterior o que han experimentado tratamientos y se los incluye si cumplen con los siguientes criterios de inclusión y exclusión:

Criterios para la Inclusión de Sujetos:

- Sujetos con diagnóstico de infección por HIV-1 que no han recibido tratamiento anterior o que han experimentado tratamientos
- HIV-ARN por el análisis Amplicor, Versión 1,5 de más de 500 copias/ml
- Recuento de CD_4^+ superior a 100 copias/ml, preferentemente superior a 200 células /ml.
- Sujetos con buen estado de salud física con resultados de análisis de laboratorio de seguridad y ECG clínicamente aceptables.
- Se deben cumplir con los siguientes parámetros:
 - Recuento de plaquetas $\geq 75,00/\text{ml}$
 - Hemoglobina $\bullet 9 \text{ g/dl}$ (90 g/l)
 - Recuento de neutrófilos absoluto $\bullet 1500 /\mu\text{l}$
 - Creatinina $< 1,5$ veces el límite máximo de lo normal
 - SGOT/SGPT ≤ 5 x el límite máximo de lo normal
 - Bilirrubina $\leq 2,5$ x el límite máximo de lo normal
- Test de embarazo por orina negativo (sólo mujeres)

Los sujetos deben estar dispuestos y ser aptos para dar consentimiento por escrito y poder ajustarse al plan desarrollado en el protocolo.

Criterios para la Exclusión de Sujetos:

- Mujeres que están amamantando o embarazadas o que no utilizan control de la natalidad adecuado.

- Sujetos con alergia a las proteínas de E. coli
- Sujetos con una historia clínica médico/ psiquiátrica significativa, específicamente con depresión o demencia.

Los sujetos son elegidos al azar para recibir interferón alfa pegilado 2b, es decir PEG₁₂₀₀₀-interferón alfa 2b, en dosis de entre 0,5 y 4,5 microgramos por kilogramo, por ejemplo en dosis de 0,5, 1,0, 1,5, 3,0 ó 4,5 microgramos por kilogramo por inyección subcutánea una vez por semana. También se puede dar comienzo a la HAART antes o simultáneamente con la administración del interferón alfa pegilado 2b, es decir, PEG₁₂₀₀₀-interferón alfa 2b, es decir PEG-Intron comercializado por Schering Corp., Kenilworth, NJ.

Diseño General y Plan del Estudio:

El objetivo fundamental de eficacia consiste en reducir los niveles plasmáticos de HIV-1-ARN en un factor de $\geq 0,5 \log_{10}$.

Los análisis de HIV-1-ARN/qPCR se realizan en un laboratorio centralizado. En la línea de base se necesita un resultado positivo del ensayo de HIV-1-ARN; sólo los pacientes con HIV-1-ARN positivo pueden participar.

ESTUDIO NO. 2

Objetivos del Estudio

Los objetivos de este estudio consisten en investigar: (i) la actividad antiviral de diversas dosis de PEG-Intron en sujetos infectados con el HIV-1 que han experimentado tratamientos y que no prosperan en el régimen antirretroviral (anti HIV-1) actual, (ii) la actividad antiviral del PEG-Intron en sujetos que comienzan un nuevo régimen de HAART optimizado tras abortar su régimen anterior y (iii) la seguridad, tolerabilidad y farmacocinética del PEG-Intron.

Diseño del Estudio

Este es un estudio aleatorio, doble ciego, de grupos paralelos, con placebos como control, de múltiples centros, de eficacia y seguridad de Fase II en sujetos infectados con HIV-1 con experiencia en tratamientos. Los individuos que obtienen una reducción de $\geq 0,5 \log_{10}$ en el HIV ARN en la semana 4 continúan su régimen con PEG-Intron con la adición de la nueva HAART optimizada durante 24 semanas más. Todos los demás pacientes son descartados, aunque se les pide que regresen para estudios de carga viral y de subseries de linfocitos de seguimiento en la Semana 16 y la Semana 28. A los sujetos que aleatoriamente fueran asignados al grupo con placebo se les ofrecerá el uso humanitario de PEG-Intron una vez que se haya determinado la dosis óptima de PEG-Intron.

Duración del Estudio

El PEG-Intron se administra por vía subcutánea una vez por semana durante hasta 28 semanas. Debe haber un período de seguimiento de 4 semanas con posterioridad al tratamiento.

Población en Estudio

La población en estudio debe incluir un total de 300 sujetos de sexo masculino y femenino con infección documentada por HIV-1 que han sido tratados continuamente con terapia antirretroviral combinatoria durante por lo menos seis meses anteriores al ingreso al estudio. Como regla general, los pacientes deben tener un estado de salud razonablemente satisfactorio con un puntaje en la Escala de Rendimiento de Karnofsky de ≥ 70 . Los pacientes deben cumplir con los criterios de Inclusión y Exclusión enumerados a continuación.

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distribución aleatoria) que pueda influenciar el nivel plasmático de HIV ARN.

- El uso de corticoesteroides sistémicos (excluyendo los agentes anabólicos), inmunosupresores, ribavirina o agentes citotóxicos (incluyendo la hidroxiurea) en un lapso de 2 semanas previas a la distribución aleatoria.

Además, el fármaco en estudio se detendrá y los sujetos serán separados del estudio en las siguientes situaciones. Evaluaciones de línea de base fuera del rango permitido en el protocolo; imposibilidad de obtener una reducción de por lo menos $0,5 \log_{10}$ en el HIV ARN en la Semana 4; uso de una medicación excluida por el protocolo; matriculación del sujeto en otra prueba de fármaco en investigación en cualquier momento durante el estudio; eventos adversos médicamente graves o con riesgo de vida; falla virológica definida en el protocolo; embarazo durante la fase de tratamiento; falta de acatamiento de la dosificación (según lo definido en el protocolo); falta de voluntad del sujeto para continuar.

Asignación al Método de Tratamiento (Distribución Aleatoria)

Los sujetos que cumplan los criterios para su ingreso serán asignados de manera aleatoria a uno de cinco grupos de tratamiento en una proporción de 1:1:1:1:1.

Tratamientos del Estudio

Los sujetos serán asignados en forma aleatoria a uno de los siguientes grupos de tratamiento:

- PEG-INTRON, $0,5 \mu\text{g/kg}$ una vez por semana SC
- PEG-INTRON, $1 \mu\text{g/kg}$ una vez por semana SC
- PEG-INTRON, $1,5 \mu\text{g/kg}$ una vez por semana SC
- PEG-INTRON, $3 \mu\text{g/kg}$ una vez por semana SC

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- PEG-INTRON placebo una vez por semana SC

Todas las inyecciones de PEG-Intron a utilizar en este estudio se prepararán con no más de 24 horas de anticipación con respecto a la administración (siempre que la dosis se mantenga refrigerada). El PEG-Intron es suministrado por Schering Corp. Kenilworth, NJ 07033 en forma de polvo liofilizado y se debe preparar de la siguiente manera:

De un frasco/ ampolla de Agua Estéril para Inyección, se retira 0,7 ml con una jeringa (por ejemplo, media pulgada, aguja calibre 27 en una jeringa de 1,0 ml). Se introduce el agua estéril en el frasco que contiene el polvo liofilizado de PEG-Intron y se mezcla suavemente. Se inspecciona el frasco para detectar decoloración o materia en partículas y, en caso de haberla, se lo descarta. El día 1 de cada semana se inyecta PEG-Intron por vía subcutánea rotando los sitios de inyección según la necesidad. Los pacientes recibirán una inyección por semana de PEG-Intron o placebo durante hasta 52 semanas.

Administración de la Medicación del Estudio

PEG-Intron/ Placebo . La dosificación se debe calcular sobre la base de $\mu\text{g/kg}$ utilizando el peso en la visita de la Línea de Base y se debe administrar por vía subcutánea (SC). Los sujetos recibirán PEG-Intron el mismo día de la semana todas las semanas.

Los sujetos pueden recibir acetaminofeno (500 – 1000 mg) 30 minutos antes de recibir PEG-Intron.

Puntos Finales Primarios

El punto final primario consistirá en el cambio medio de HIV ARN desde la línea de Base a la Semana 4 de la terapia con PEG-Intron. El HIV ARN de la Línea de Base debe ser la media de 2 valores de ARN, uno obtenido 7 – 14 días antes de iniciarse con la droga en estudio y el otro obtenido inmediatamente antes de la primera dosis de la droga en estudio.

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Puntos Finales Secundarios

Los puntos finales secundarios incluyen los siguientes: ABC para el HIV ARN desde la Línea de Base a la Semana 4; cambio en el recuento absoluto de CF_4^+ y porcentaje desde la Línea de Base a la Semana 4; cambio de marcadores de activación de células T desde la Línea de Base a la Semana 4. Asimismo, se estudiarán los siguientes parámetros: cambio en la carga viral (y ABC) en las semanas 12 y 24 después de iniciar la nueva HAART optimizada; cambio en el recuento absoluto de CF_4^+ y porcentaje en las semanas 12 y 24 después de iniciar la nueva HAART optimizada; tiempo transcurrido hasta la declinación del HIV ARN por debajo del límite de cuantificación del ensayo después de iniciar la nueva HAART optimizada y cambio en el perfil de resistencia al HIV de los componentes individuales del régimen de HAART de cada sujeto a las 24 de la nueva HAART optimizada o en el momento de la falla virológica (lo que ocurra en primer lugar).

Evaluaciones de Laboratorio

Se utilizará un laboratorio central para las pruebas clínicas de laboratorio durante el estudio. Se utilizarán los resultados de la Línea de Base obtenidos en el laboratorio central como base para determinar se ha producido un cambio clínicamente significativo en una variable de seguridad después de la primera dosis de la medicación en estudio. Si es necesario, se deben realizar en el laboratorio central otras evaluaciones de laboratorio necesarias para la seguridad del sujeto durante el estudio. Si esto no es posible, se aceptan laboratorios locales.

ESTUDIO NO. 3

Objetivos del Estudio

Los objetivos de este estudio de dosis múltiple en aumento, de rótulo abierto son: (1) evaluar la seguridad y tolerabilidad de dosis únicas y múltiples

de PEG-Intron en pacientes pediátricos con infección crónica por HIV que puedan tener resistencia a la terapia antirretroviral en curso, utilizando un diseño de estudio de dosis en aumento; (2) medir la farmacocinética de dosis simples y múltiples de PEG-Intron en pacientes pediátricos con infección crónica por HIV y (3) examinar el efecto del PEG-Intron en la farmacodinámica viral del HIV (recuentos de HIV-ARN, CD_4^+) y los parámetros inmunes.

Diseño del Estudio

Este es un estudio de seguridad, tolerabilidad, farmacocinética y farmacodinámica de Fase I, de rótulo abierto de dosis múltiples en aumento, sin controles llevado a cabo en sujetos pediátricos con infección crónica por HIV-I. Este estudio también está destinado a determinar la toxicidad limitante de la dosis (TLD) y la dosis máxima tolerada (DMT) de PEG-Intron en niños administrada una vez por semana durante 4 semanas.

Duración del Estudio

El tratamiento del estudio se administra una vez por semana durante 4 semanas.

Población del Estudio

En este estudio se pueden anotar pacientes pediátricos infectados con HIV de sexo masculino y/o femenino entre 3 y 16 años de edad. Los pacientes deben tener infección de HIV crónica durante > 1 año. Los pacientes deben estar ya establecidos en una terapia antirretroviral con títulos detectables (> 500 copias/ ml) de HIV ARN. No se permitirá cambiar el régimen antirretroviral dentro de las 6 semanas del ingreso al estudio o durante el tiempo que reciben PEG-Intron. Los pacientes deben cumplir con los Criterios de Inclusión y Exclusión enumerados a continuación:

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Criterios de Inclusión de Sujetos

Los sujetos deben estar generalmente en buen estado físico de salud con resultados de análisis de seguridad de laboratorio aceptables y ECG normal.

- Sujetos entre los 3 y 16 años de edad, con infección crónica por HIV-I en un régimen antirretroviral estable durante por lo menos 6 semanas. Los sujetos deben persistir en su régimen antirretroviral durante la duración del estudio.
- niveles de HIV-ARN por el Amplicor de más de 500 copias/ml
- Recuentos de CD_4^+ superiores a 200 células /ml (Categoría Inmunológica CDC 1 ó 2).
- Ausencia de infección sistémica oportunista activa determinada en el examen físico.
- Ninguna historia de infección oportunista sistémica o inmunización en los 2 meses precedentes.
- Se deben cumplir con los siguientes parámetros de laboratorio:
 - Recuento de plaquetas $\geq 75,000/\mu l$ ($75 \times 10^9/l$)
 - Hemoglobina ≥ 9 g/dl (90 g/l)
 - Recuento de neutrófilos absoluto $\geq 1500 /\mu l$ ($0,15 \times 10^9/l$)
 - Creatinina $< 1,5$ veces el límite máximo de lo normal
 - SGOT/SGPT ≤ 5 x el límite máximo de lo normal
 - Bilirrubina $\leq 2,5$ x el límite máximo de lo normal
- Test sérico de embarazo negativo (sólo mujeres)
- Los padres/ tutores deben entregar un consentimiento informado por escrito, también se dará consentimiento informado por escrito

a los niños con capacidad para hacerlo. Todos los participantes deben poder ajustarse al plan desarrollado en el protocolo.

Criterios para la Exclusión de Sujetos:

- Sujetos con trastornos de consideración clínica no relacionados con su enfermedad por HIV.
- Progreso del HIV-I a SIDA
- Mujeres que están amamantando o embarazadas o no están utilizando control de la natalidad adecuado
- Individuos que han participado en un ensayo clínico de una droga en investigación el mes anterior
- Sujetos que dan positivo para el antígeno superficial de la hepatitis B o el anticuerpo de la hepatitis C.
- Sujetos con alergia a las proteínas de E. coli.
- Sujetos con historia médico/ psiquiátrica significativa, especialmente con depresión.
- Presencia de anticuerpos neutralizantes del Interferón (es posible que no se disponga de estos resultados durante el screening; los pacientes serán considerados para su admisión sin estos resultados).
- Pacientes con historia clínica de droga-dependencia.

Método de Asignación al Tratamiento (Distribución aleatoria)

Se asignan números a los pacientes en forma centralizada. La asignación al tratamiento no es aleatoria en este estudio.

Cuatro series de sujetos recibirán PEG-Intron en dosis de 0,75, 1,5, 3,0 o 4,5 µg/kg por inyección subcutánea una vez por semana (QW) durante 4 semanas.

La serie de paciente se enrola en un nivel de dosificación de 0,75 µg/kg. Las series de pacientes posteriores se enrolarán en dosis sucesivamente más elevadas de acuerdo con los lineamientos de escala de dosificación expuestos a continuación.

Tratamientos del Estudio

PEG-Intron: 0,75, 1,5, 3,0 o 4,5 µg/kg SC, QW

Todas las inyecciones de PEG-Intron a utilizar en este estudio se prepararán con no más de 24 horas de anticipación con respecto a la administración (siempre que la dosis se mantenga refrigerada). El PEG-Intron se obtiene en forma de polvo liofilizado y se debe preparar de la siguiente manera:

De un frasco/ ampolla de Agua Estéril para Inyección, se retira 0,7 ml con una jeringa (por ejemplo, 5/8 pulgada, aguja calibre 25 en una jeringa de 1,0 ml). Se introduce el agua estéril en el frasco que contiene el polvo liofilizado de PEG-Intron y se mezcla suavemente. Se inspecciona el frasco para detectar decoloración o materia en partículas y, en caso de haberla, se lo descarta. 0,5 ml de esta solución contiene 50 µg, 100 µg, 150 µg ó 300 µg de PEG-Intron dependiendo del frasco empleado. El día 1 de cada semana se inyecta PEG-Intron por vía subcutánea rotando los sitios de inyección según la necesidad. Los pacientes recibirán una inyección semanal de PEG-Intron durante 4 semanas.

Los volúmenes de dosificación se calcularán empleando la siguiente fórmula:

Volumen = peso corporal x dosis/ concentración de PEG-Intron

- Para la dosis de 0,75 µg/kg, empleando un tamaño de frasco de un tamaño de 50 µg.

Volumen (ml) = peso corporal (kg) x 0,75 µg/ kg/100 µg/ml

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- Para la dosis de 1,5 µg/kg, empleando un tamaño de frasco de un tamaño de 100 µg.

$$\text{Volumen (ml)} = \text{peso corporal (kg)} \times 1,5 \mu\text{g/kg} / 200 \mu\text{g/ml}$$

- Para la dosis de 3,0 µg/kg, empleando un tamaño de frasco de un tamaño de 150 µg.

$$\text{Volumen (ml)} = \text{peso corporal (kg)} \times 3,0 \mu\text{g/kg} / 300 \mu\text{g/ml}$$

- Para la dosis de 4,5 µg/kg, empleando un tamaño de frasco de un tamaño de 300 µg.

$$\text{Volumen (ml)} = \text{peso corporal (kg)} \times 4,5 \mu\text{g/kg} / 300 \mu\text{g/ml}$$

Todas las dosis de PEG-Intron se deben administrar en la clínica bajo la dirección del personal a cargo del estudio.

Durante las primeras 48 horas de la terapia, el sujeto debe poder acceder fácilmente al médico del estudio, al coordinador médico o al personal de enfermería ya que los eventos adversos son típicamente los más severos después de la primera inyección. Se pueden síntomas gripales, fiebre, escalofríos, fatiga y malestar en sujetos dos a ocho horas tras la dosis inicial de la medicación del estudio. Las reacciones iniciales son generalmente de carácter leve a moderado y, en la mayoría de los sujetos se origina la taquifilaxis de estos síntomas.

Para pacientes que completan todos los procedimientos de la Semana 4, y que, a criterio del Investigador se pueden beneficiar con la continuación del tratamiento, se puede continuar con el tratamiento con PEG-Intron después del estudio en un estudio de continuación. Durante el tratamiento compasivo, El Director de Investigaciones monitoreo de los parámetros de seguridad, tolerabilidad, virología e inmunológicos.

Puntos Finales Primarios

Los siguientes son los puntos finales primarios:

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- Pruebas de Laboratorio de Seguridad, signos vitales, ECG y eventos adversos informados durante las 4 semanas de tratamiento.
- Título de HIV-ARN en suero y recuentos de células CD_4^+ durante las 4 semanas de tratamiento.
- Concentraciones séricas de PEG-Intron en dosis simples y múltiples (Semanas 1 y 4).

El objetivo fundamental de este estudio es describir la seguridad y tolerabilidad del PEG-Intron sobre la base de los datos obtenidos de las 4 semanas de tratamiento. Los datos de concentración y los parámetros farmacocinéticos obtenidos (ABC y $C_{m\acute{a}x}$) del PEG-Intron, y los títulos de HIV-ARN se resumen utilizando estadísticas descriptivas. Además de los análisis especificados a continuación, se presentan listados de todos los datos correspondientes a cada paciente.

Se utilizan los recuentos de HIV-ARN y CD_4^+ de pretratamiento (Días -28, -2 y Día 1, hora 0) como Líneas de Base para cada individuo. Con relación al valor de la Línea de Base, la evidencia de la respuesta al Interferón se basa en la reducción de HIV-ARN de $> 0,5$ log.

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Tabla I

DOSAJE Y REGIMEN DE DOSAJE DE INHIBIDORES NUCLEOSÍDICOS DE
LA TRANSCRIPTASA INVERSA (NRTI)

NRTI (nombre comercial, Proveedor	Dosaje habitual para adultos
Zidovudina, (AZT (Retrovir – Glaxo Wellcome)*	200 mg PO tres veces/ día o 300 mg PO dos veces/ día
Stavudina (Zerit – Bristol-Myers Squibb)*	40 mg PO dos veces/ día ¹
Didanosina (Videx – Bristol-Myers Squibb)*	200 mg PO dos veces/ día ²
Lamivudina (Epivir - Glaxo Wellcome)*	150 mg PO dos veces/ día ³
Zalcitabina (Hivid – Roche)	0,75 mg PO tres veces/ día
Zidovudina más lamivudina (Convivir - Glaxo Wellcome)	1 tableta PO dos veces/ día ⁴
Abacavir (Ziagen - Glaxo Wellcome)	200 ó 400 mg PO tres veces/ día
Adefovir dipivoxil (Prevon . Sciences)	125 ó 200 mg PO diarios ⁵
Lobucavir (BMS.170194 – BMS)	200 mg PO dos veces/ día ⁶
BCH . 10652 (Biochem Pharma)	400 mg PO, diarios ⁷
Emitricitabina ((-)-FTC- Pharmaceuticals)	200 mg PO diarios ⁸
Beta-L-FD4 (B-L-DrC – Pharmaceutical)	0,2 – 25 mg/kg/ día ⁹
DAPD (Triangle Pharmaceuticals)	_____ ¹⁰
Lodenasina (FddA- U.S. Bioscience)	1,6 – 3,2 mg/kg PO dos veces/ día ¹¹

Notas al Pie de Tabla I

* Disponible en formulación líquida

¹ Para pacientes de menos de 60 kg, 30 mg PO dos veces por día.

² Con tabletas; para pacientes < 60 kg, 125 mg PO dos veces diarias; > 60 kg, 200 mg PO dos veces diarias. Con polvo, el dosaje varía de 167 mg (< 60 kg) a 250 mg PO (> 60 kg) dos veces por día. Las dosis se deben tomar por lo menos 30 minutos antes de las comidas o por lo menos dos horas después.

³ Para pacientes de menos de 50 kg, 2 mg/kg PO dos veces diarias.

⁴ Cada tableta contiene 300 mg de zidovudina y 150 mg de lamivudina.

⁵ Disponible bajo un programa de acceso expandido – Una Prueba de Fase II patrocinada por el NIH

⁶ Fase II.

⁷ Fase I/II; ver PharmaProjects, secciones J5A & J5Z.

⁸ Fase I/II; ver PharmaProjects, secciones J5A & J5Z

⁹ Preclínica; activa en modelo de HBV en patos, ver PharmaProjects, secciones J5A & J5Z.

¹⁰ Preclínica; activa po e IV; DAPD es un profármaco de otra purina de dioxoleno, DXG. Ver PharmaProjects, secciones J5A & J5Z

¹¹ Fase II, FDA tiene potencial para dosis diaria.

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Tabla II

DOSAJE Y REGIMEN DE DOSAJE DE INHIBIDORES NO NUCLEOSÍDICOS
DE LA TRANSCRIPTASA INVERSA (NNRTI)

NNRTI (nombre comercial, Proveedor	Dosaje habitual para adultos y Régimen de Dosaje
Nevirapina (Viramune – Roxane)	200 mg PO dos veces/ día ¹
Delavirdina (Rescriptor – Pharmacia & Upjohn	400 mg PO tres veces/ día
Efavirenz (Sustiva, Dupont)	200 mg PO diarios ²
PNU-142721 (Pharmacia + Upjohn)	_____ ³
AG-1549 (Agouvon Pharmaceuticals)	_____ ⁴
MKC-442 (Triangle Pharmaceuticals)	750 mg PO dos veces/ día ⁵
(+)-Calanolida A (Med. Chem. Research)	800 mg PO ⁶

¹ Durante las primeras dos semanas de tratamiento con nevirapina, para reducir el riesgo de erupciones, los pacientes deben tomar sólo una tableta diaria de 200 mg.

² Terapia Cuádruple de efavirenz con indinavir + 2 NRTI o Terapia Triple de efavirenz + AZT + lamivudina.

³ Fase Preclínica; ver PharmaProjects, secciones J5A & J5Z

⁴ Fase I/II. Se evalúa la dosis y el uso simultáneo de otras terapias contra el HIV; ver PharmaProjects, secciones J5A & J5Z

⁵ Terapia Triple de (a) MKC-442 con estavudina y lamivudina o didanosina o (b) MKC-442 con nelfinavir (qv) y NRTIs.

⁶ Fase I; ver PharmaProjects, secciones J5A & J5Z

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Tabla III

DOSAJE Y REGIMEN DE DOSAJE DE INHIBIDORES DE LA PROTEASA

PI (nombre comercial, Proveedor	Dosaje + Régimen de Dosaje
Saquinavir (invirase – cápsula de 600 mg PO tres veces por día ¹ gelatina dura – Roche) (Fortovase – 1100 mg PO tres veces por día ¹ cápsula de gelatina blanda – Roche)	
Ritonavir (Norvir – Abbott)	600 mg PO dos veces por día ²
Indinavir (Crixivan – Merck)	800 mg PO diarios ³
Nelfinavir (Viracept – Agouron)	750 mg PO tres veces por día ⁴
Amprenavir (141W94, Glaxo)	900 mg – 1200 mg PO dos veces por día ⁵
Lasinavir (BMS – 234475, BMS)	6
DMP-450 (Triangle Pharmaceuticals)	7
BMS-2322623 (BMS)	8
ABT-378 (Abbott)	60 mg PO dos veces por día ⁹

¹ Con una comida o dentro de las dos horas de ingerida la misma

² Con alimentos. La preparación líquida tiene sabor desagradable. El fabricante sugiere tomarla con leche chocolatada o con un suplemento alimenticio líquido.

³ Con agua, una hora antes o dos horas después de una comida. Los pacientes que toman indinavir deben beber por lo menos 48 onzas (1,5 litro) de agua por día.

⁴ Con alimentos.

⁵ Terapia Combinatoria Cuádruple de amprenavir con AZT + lamivudina + abacavir.

⁶ Fase I/II; ver PharmaProjects, secciones J5A & J5Z.

⁷ Fase II; ver PharmaProjects, secciones J5A & J5Z.

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⁸ Estudios preclínicos; los ésteres profármacos de BMS 2322623 aumentan la absorción oral; ver PharmaProjects, secciones J5A & J5Z.

⁹ Los estudios de Fase I demuestran que el ABT-378 es 10 veces más potente que el ritonavir; ver PharmaProjects, secciones J5A & J5Z.

Tabla IV

OTRAS DROGAS ANTI-HIV

Droga (nombre comercial, Proveedor	Dosaje habitual para adultos y
	Régimen de Dosaje
Hidroxiurea (Droxia, BMS)	1000 mg PO por día ¹
Ribavirina (Rebetol, Schering Plough)	600 mg - 1200 mg/día, PO
IL-2 (Proleukin, Chiron Corp.)	1 – 2 millones UI/ día, sc
IL-12 (Roche)	0,5 – 10 microgramos/ kg/ día, sc
Yissum Project No. 11607	_____ ²

¹ Terapia triple con hidroxiurea con 400 mg ddl + 500 mg de AZT; ver PharmaProjects, sección B3C1

² Preclínica; ver PharmaProjects, secciones J5A & J5Z.

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REIVINDICACIONES

1. El uso de interferón alfa pegilado para la preparación de un medicamento para el tratamiento de infecciones por HIV-1 en pacientes.
2. El uso de acuerdo con la reivindicación 1 en el cual el interferón alfa-2b se administra en combinación con una cantidad terapéuticamente efectiva de por lo menos uno entre ribavirina, IL-2, IL-12 y pentafusida solo o en combinación con una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1.
3. El uso de una farmacoterapia contra el HIV-1 e interferón alfa pegilado para la preparación de un medicamento para el tratamiento de infecciones por HIV-1 en pacientes.
4. El uso de acuerdo con la reivindicación 2 ó 3 en el cual la farmacoterapia contra el HIV es HAART.
5. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el tratamiento comprende una cantidad terapéuticamente efectiva de interferón alfa pegilado y una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1 suficiente para reducir los niveles detectables de HIV-1-ARN en esos pacientes.
6. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual los pacientes son pacientes que han experimentado tratamientos o pacientes que se someten a tratamiento por primera vez.
7. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual los pacientes son pacientes pediátricos que han experimentado tratamientos o pacientes que se someten a tratamiento por primera vez.

8. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el interferón alfa pegilado es interferón alfa-2a pegilado o interferón alfa-2b pegilado

9. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el interferón alfa pegilado es interferón alfa-2b pegilado y donde el tratamiento comprende una cantidad de aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo en una sola dosis por semana o en dosis divididas dos veces por semana, preferentemente en el rango de aproximadamente 0,5 a aproximadamente 3,0 microgramos por kilogramo en una sola dosis por semana o en dosis divididas dos veces por semana y más preferentemente en el rango de aproximadamente 0,75 a aproximadamente 1,5 microgramos por kilogramo en una sola dosis por semana o en dosis divididas dos veces por semana.

10. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el interferón alfa pegilado es interferón alfa-2b pegilado y donde el tratamiento comprende interferón alfa-2b pegilado en combinación con una farmacoterapia contra el HIV-1, que es preferentemente HAART.

11. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el interferón alfa pegilado es interferón alfa-2a pegilado y el tratamiento comprende una cantidad de interferón alfa-2a pegilado administrado en el rango de aproximadamente 50 a aproximadamente 500 microgramos en una sola dosis por semana o en dosis divididas dos veces por semana, preferentemente en el rango de aproximadamente 200 a aproximadamente 250 microgramos en una sola dosis por semana o en dosis divididas dos veces por semana.

12. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el paciente está coinfectado con el HCV.

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13. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el tratamiento comprende interferón pegilado administrado una vez por semana o dos veces por semana durante por lo menos 2 a 4 semanas antes de la administración de una cantidad terapéuticamente efectiva de por lo menos uno entre ribavirina, IL-2, IL-12 y pentafusida solo o en combinación con una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1 y, preferentemente, donde la farmacoterapia contra el HIV-1 es HAART.

14. El uso de acuerdo con cualquiera de las reivindicaciones precedentes en el cual el tratamiento comprende (1) de aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado en una sola dosis semanal o en dosis divididas dos veces por semana en un primer período de tiempo de tratamiento de aproximadamente dos a aproximadamente cuatro semanas, seguido por (2) una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1 en combinación con aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo de interferón alfa-2b pegilado administrado en una sola dosis semanal o en dosis divididas dos veces por semana en un segundo período de tratamiento suficiente para reducir los niveles detectables de HIV-1-ARN.

15. El uso de acuerdo con la reivindicación 7, en el cual el interferón alfa pegilado es interferón alfa-2b pegilado y donde el tratamiento comprende una cantidad de interferón alfa-2b pegilado administrado en el rango de aproximadamente 0,1 a aproximadamente 9,0 microgramos por kilogramo por semana, preferentemente en el rango de aproximadamente 0,5 a aproximadamente 4,5 microgramos por kilogramo en una sola dosis por semana o en dosis divididas dos veces por semana y más preferentemente en el rango de aproximadamente 2,25 a aproximadamente 2,6 microgramos por

kilogramo en una sola dosis por semana o en dosis divididas dos veces por semana.

16. El uso de acuerdo con la reivindicación 7, en el cual el interferón alfa pegilado es interferón alfa-2a pegilado y el tratamiento comprende una cantidad de interferón alfa-2a pegilado en el rango de aproximadamente 50 a aproximadamente 500 microgramos en una sola dosis por semana o en dosis divididas dos veces por semana, o preferentemente en el rango de aproximadamente 150 a aproximadamente 190 microgramos en una sola dosis por semana o en dosis divididas dos veces por semana.

17. El uso de acuerdo con la reivindicación 7, en el cual el paciente pediátrico está coinfectado con HCV y el tratamiento comprende además ribavirina administrada al paciente pediátrico en combinación con el interferón alfa pegilado y donde la cantidad de ribavirina está en el rango de aproximadamente 8 a aproximadamente 15 mg por kilogramo por día, en dosis divididas.

18. El uso de acuerdo con la reivindicación 7, en el cual el tratamiento comprende además una hormona de crecimiento humana en combinación con una farmacoterapia contra el HIV-1 y un interferón alfa pegilado.

19. El uso de acuerdo con la reivindicación 18, en el cual el paciente pediátrico está coinfectado con HCV y HIV-1 y el tratamiento comprende asimismo ribavirina.

20. El uso de acuerdo con la reivindicación 7, en el cual el tratamiento comprende además una hormona de crecimiento humana administrada en combinación con una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1 y una cantidad terapéuticamente efectiva de interferón alfa pegilado y una cantidad terapéuticamente efectiva de ribavirina.

RESUMEN DE LA DESCRIPCIÓN

Se describen los usos del interferón alfa, solo y en combinación con una farmacoterapia contra el HIV-1 y la ribavirina para la preparación de un medicamento para el tratamiento de pacientes que no han experimentado tratamientos y pacientes adultos y pediátricos infectados por el HIV-1 que han experimentado tratamientos así como pacientes coinfectados con HIV-1 y HCV, que comprende una cantidad terapéuticamente efectiva de interferón alfa pegilado, por ejemplo interferón alfa-2b pegilado, como monoterapia o, preferentemente, en combinación con una cantidad terapéuticamente efectiva de por lo menos una entre ribavirina, IL-2, IL-12 y pentafusida sola o en combinación con una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1, por ejemplo HAART.

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EXTRACTO PARA PUBLICACION
SOLICITUD DE PATENTE DE INVENCION

DELEGATURA PROPIEDAD INDUSTRIAL

(21) No. SOLICITUD: 00-14824 (51) INT. CL. A 61K 38/21
(22) FECHA DE PRESENTACION: 00-03-01 (71) SOLICITANTE: SCHERING-CORPORATION
(30) PRIORIDAD: si
(31) No. DE SOLICITUD: 09/260,388 (72) INVENTOR/ES : MARK A. LAUGHLIN, PAUL W.
09/268,521; 09/288,358; 09/454,004 GLUE, CARLOS O. STANGIS.
(32) FECHA DE PRESENTACION: 02-03-99; (74) APODERADO: CARLOS R. OLARTE
12-03-99; 08-04-99; 03-12-99
(33) PAIS: US/US/US/US

(54) TITULO : TERAPIA CONTRA EL HIV.

(57) RESUMEN :

Se describen los usos del interferón alfa, solo y en combinación con una farmacoterapia contra el HIV-1 y la ribavirina para la preparación de un medicamento para el tratamiento de pacientes que no han experimentado tratamientos y pacientes adultos y pediátricos infectados por el HIV-1 que han experimentado tratamientos así como pacientes coinfectados con HIV-1 y HCV, que comprende una cantidad terapéuticamente efectiva de interferón alfa pegilado, por ejemplo interferón alfa-2b pegilado, como monoterapia o, preferentemente en combinación con una cantidad terapéuticamente efectiva de por lo menos una entre ribavirina, IL-2, IL-12 y pentafusida sola o en combinación con una cantidad terapéuticamente efectiva de una farmacoterapia contra el HIV-1, por ejemplo HAART.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00014824 00000000 Folios: 237
Fecha (AND): 2000-03-01 17:03:17
Tramite : 002 PATENTES D 1 REGISTRO/ 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PATENTE DE INVENCION ☒

MODELO DE UTILIDAD []

- Nombre e identificación del Solicitante []
- Nombre e identificación del Inventor []
- Título o nombre de la Invención []
- Descripción []
- Reivindicaciones []
- Resumen []
- Comprobante de Pago []

COMPLETA ☒

INCOMPLETA []

DISEÑO INDUSTRIAL []

- Nombre e identificación del peticionario []
- Nombre e identificación del inventor o diseñador []
- Indicación del género de productos para los cuales debe utilizarse []
- Representación gráfica []
- Comprobante de pago []

COMPLETA []

INCOMPLETA []


Firma Responsable

Fecha: _____

DIVISION DE NUEVAS CREACIONES

PRIMER EXAMEN DE FORMA

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2000-03-02 229

EXPEDIENTE 0-014824

Practicado el examen jurídico de acuerdo con lo establecido en el art. 21 de la Decisión 344 se determinó que esta solicitud de **Patente de Invención**:

SI ☒ NO ☐ **NO APLICABLE** ☐ Presentó los poderes necesarios en forma correcta (Decisión 344, art. 14-a).

SI ☒ NO ☐ **NO APLICABLE** ☐ Acreditó, en forma correcta, la existencia y representación de la persona jurídica solicitante (art. 14-c de la Decisión 344; literal g) del art. 4 del Decreto 117/94).

SI ☒ NO ☐ **NO APLICABLE** ☐ Presentó, en forma correcta, el comprobante de pago por la tasa de presentación establecida (art. 13-f de la Decisión 344 y la Resolución 02 del 4 de enero del 2000).

SI ☒ NO ☐ **EXTEMPORANEAMENTE** ☐ Reivindicó prioridad, dentro del plazo y de acuerdo con lo previsto en el Artículo 4 del Convenio de París.

SI ☒ NO ☐ **NO APLICABLE** ☐ Presentó copia, certificada su conformidad por la Administración que recibió la solicitud de la cual reivindica prioridad, al momento de radicar la solicitud nacional.

SI ☐ NO ☒ **NO APLICABLE** ☐ Presentó la traducción del capítulo reivindicatorio de la solicitud de la cual se reivindica prioridad (Art. 4, D-3 Convenio de París; Concepto: 5 de enero de 1999 S.I.C.).

SI ☐ NO ☒ **CUMPLE LOS REQUISITOS JURIDICOS**

OBSERVACIONES JURIDICAS CONVENIO DE PARIS: De acuerdo con lo previsto en el artículo 4 D 3 del Convenio de París, "los países de la Unión podrán exigir de quien haga una declaración de prioridad la presentación de una copia de la solicitud (descripción, dibujos, etc.) depositada anteriormente. Se podrá exigir que vaya acompañada de un certificado de la fecha del deposito expedido por dicha Administración y de una traducción". Concordante con lo anterior el artículo 13 numeral d) de la Decisión 344 exige la **presentación de una o más reivindicaciones** dentro del contenido de la solicitud presentada ante la oficina nacional competente. De lo que se concluye que una cosa es la traducción del capítulo reivindicatorio de la copia de la solicitud de la cual reivindica prioridad y otra diferente son las reivindicaciones contenidas en la solicitud nacional, las cuales es necesario confrontar y en todo caso deben coincidir. En conclusión, deberá presentarse la traducción de los capítulos reivindicatorios de las copias, certificadas su conformidad por la Administración que recibió las solicitudes de la cuales reivindica prioridad, **en cualquier momento dentro del plazo de tres (3) meses** contados a partir de la fecha de depósito de la solicitud posterior. La omisión de esta formalidad implicará la pérdida del derecho de prioridad.

**CONTINUACION DEL PRIMER EXAMEN DE FORMA JURIDICO.
EXPEDIENTE 0-014824**

OTRAS OBSERVACIONES: La fecha correcta del depósito de la solicitud estadounidense 09/268,521 es el día 12 de marzo de 1999 (folio 37) y no el día 9 de septiembre de 1999 según se indicó en el folio 1 de la solicitud nacional.

En consecuencia, se conceptúa que esta solicitud:

SI [] NO [x] Se ajusta a los aspectos FORMALES indicados en la Decisión 344 y por tanto,

SI [] NO [x] Se recomienda PUBLICAR el extracto correspondiente.

Santafé de Bogotá, D.C., 2 de marzo de 2000.

EXAMINADOR JURIDICO: Código 202002

HACIA ABAJO LA HOJA ESTA EN BLANCO.

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1º EXAMEN DE FORMA

Radicación no 00-14824

Concepto Técnico no 768 Clasificación Internacional de Patentes A61K 38/21

Practicado el examen de acuerdo a lo establecido en el Art. 21 de la Decisión 344 se determinó que esta solicitud de **Patente de Invención**:

- | | |
|--|--|
| SI ☒ NO ☐ | Contiene la identificación correcta del inventor (Art.8, Art.13-a). |
| SI ☒ NO ☐ | Contiene la identificación correcta del solicitante (Artículo 13-a). |
| SI ☒ NO ☐ | Contiene el resumen con el objeto y finalidad de la invención en forma correcta (Art.13-e). |
| * SI ☐ NO ☒ | Contiene el título o nombre de la invención en forma correcta (Art.13-b). |
| SI ☒ NO ☐ | Contiene la descripción clara y completa de la invención (Art.13-c). |
| SI ☒ NO ☐ | Contiene los dibujos correctos (Art.14-c junto con el literal d) del Art. 4 del Dto. 117 del 94). |
| SI ☒ NO ☐ | Contiene las unidades de medida en el sistema exigido (Art.14-c junto con el Decreto 3464 del 26 de diciembre de 1980). |
| SI ☒ NO ☐ | Contiene una o más reivindicaciones, en forma correcta, que precisen la materia para la cual se solicita la protección mediante la patente (Art.13-d). |
| * SI ☒ NO ☐ | Contiene el extracto de acuerdo con el literal c) del artículo 4 del Dto. 117 /94. |
| SI ☐ NO ☐ | Contiene el arte final del dibujo característico de acuerdo con el literal c) del artículo 4 y el artículo 27 del Dto. 117 /94. |
| * SI ☒ NO ☐ | Contiene la tarjeta del Archivo Temático [formato P-104] en forma correcta (Art.14-c junto con el literal b) del artículo 4 del Dto. 117 /94). |
| * SI ☒ NO ☐ | Contiene la tarjeta del Archivo de Propietarios [formato P-105] en forma correcta (Art.14-c junto con el literal b) del artículo 4 del Dto. 117 /94). |
| SI ☐ NO ☒ | CUMPLE LOS REQUISITOS TÉCNICOS |

OBSERVACIONES Y OTROS: SI ☒ NO ☐ ver hoja(s) anexa(s)

Santa Fe de Bogotá, D.C., Mayo 22/00

EXAMINADOR TÉCNICO

Código 202010

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DIVISIÓN DE NUEVAS CREACIONES
1º EXAMEN DE FORMA

CONCEPTO TÉCNICO N° 768

EXPEDIENTE N° 0-14824

IPC A61K 38/21

Revisar y corregir en la hoja de presentación, la fecha de presentación de la solicitud de Estados Unidos 09/268,521, de la cual se reivindica prioridad; ya que no corresponde a la fecha que aparece en la copia adjunta. Esto se presta para confusión.

- * Debe tenerse en cuenta que el título debe estar de acuerdo con el capítulo descriptivo y el reivindicatorio. Este debe definir en forma breve y precisa el objetivo de la invención para permitir ubicar al lector en el campo tecnológico de la invención. Por este motivo, es necesario que el título de la solicitud se modifique, ya que tanto en la descripción como en las reivindicaciones, se hace referencia al uso de interferón alfa pegilado para la preparación de un medicamento.

Al corregir el título, debe anexarse nuevo extracto para publicación, nueva tarjeta para el archivo temático y nueva tarjeta para el archivo de propietario.

- En el capítulo descriptivo, los folios 190 y 191 corresponden a la misma página.

Santa Fe de Bogotá D.C., 22 de mayo de 2000

Examinador Técnico de Patentes
Q.F. Cód. 202010

EXPEDIENTE 0-014824

AUTO 0604

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2000-06-08

LA JEFE DE LA DIVISION DE NUEVAS CREACIONES

DISPONE

ARTICULO PRIMERO: Reconocer personería al doctor Carlos R. Olarte, como apoderado del solicitante, en los términos y para los efectos del poder conferido

ARTICULO SEGUNDO: Conforme lo establece el artículo 22 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, requiérese al solicitante, para que dentro del plazo de treinta (30) días hábiles siguientes a la fecha de notificación del auto, presente respuesta a las observaciones o complementé los antecedentes señalados en el examen de forma.

ARTICULO TERCERO: Notificar por estado el presente auto, advirtiéndole que contra el no procede recurso alguno en la vía gubernativa.

NOTIFIQUESE Y CUMPLASE

06 JUN 2000

Dado en Santafé de Bogotá D.C., a los _____

LA JEFE DE LA DIVISION DE NUEVAS CREACIONES,

ALIX CARMENZA CESPEDES DE VERGEL

NOTIFICADO POR ESTADO

Santafé de Bogotá D.C., 08 JUN 2000 notificado por anotación en estado de esta misma fecha.

VENCIMIENTO NOTIFICACION ESTADO

SOLICITO PRORROGA TERMINO SI _____ NO _____

VENCIMIENTO TERMINO PRORROGA