



No. 07-038013-00004-0000

Fecha: 2009-03-30 14:14:50 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 100

600

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

☒ Patente de Invención.
☒ Patente de Modelo de Utilidad.
☒ Diseño Industrial.
☒ Esquema de Trazado para Circuitos Integrados.
☒ Marcas de Productos o Servicios.

☐ Marca Colectiva.
☐ Marca de Certificación.
☐ Lema Comercial.

②

SOLICITUD
PUBLICADA

Numero del expediente: 07-38013

Solicitante: GENENTECH, INC

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la nueva creación o denominación del signo: FORMULACIÓN DE
ANTICUERPO EN AMORTIGUADOR DE ACETATO DE HISTIDINA.

Gaceta: S99

③

OPOSICION PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio:	C.E. ☐	Otro ☐
	Lugar de Constitución: COLOMBIA	Cual	
	BARRANQUILLA	Número 890.106.527-5	
	Teléfono: (571)3719900 Fax: (571)3730818		
	E-mail: negocios@optimum-co.com		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISaura MORENO	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 104	C.C. ☒	NIT ☐
	Teléfono: (571) 2131213 Fax: (571) 6121979	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual	
		Número 51'975.664 83823 TP	

④

FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causa:

No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos patentabilidad
dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo
de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

607

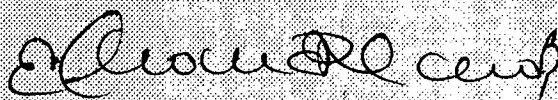
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa. ✓
- ☒ Poderes, si fuere el caso. X
- ☒ Pruebas de los fundamentos de la oposición. ✓
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso. ✓
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas. ✓

⑦

NOMBRE: ELIANA ISAURA MORENO B. ✓

FIRMA:



C.C. 51975664

TP. 83823 CSJ



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 038.013 ✓
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN DE ANTICUERPO EN
AMORTIGUADOR DE ACETATO DE HISTIDINA"
Solicitante : GENENTECH, INC
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 599 del 31 de Diciembre de 2008 ✓

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, ✓ abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de agente oficioso de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**FORMULACIÓN DE ANTICUERPO EN AMORTIGUADOR DE ACETATO DE HISTIDINA**", cuyo titular es **GENENTECH, INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular ACETATO DE HISTIDINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 17 de abril de 2007 reivindicando prioridad bajo la solicitud US20040620413P del 2004-10-26 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 529 del 31 de Diciembre de 2008, cuya publicación internacional corresponde a la WO2006044908 del 2006-04-27.

2.2. La solicitud colombiana 07 038.013 objeto de la presente oposición se refiere a una formulación farmacéutica estable que comprende un antiérgico en solución en un amortiguador de acetato de histidina, pH 5.5 a 6.5; en donde el pH es desde 5.8 a 6.2; en donde la concentración del amortiguador de acetato de histidina es desde alrededor de 1mM a alrededor de 200mM; en donde la concentración del amortiguador de acetato de histidina es desde alrededor de 10mM a alrededor de



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

40mM; en donde la concentración de anticuerpo es desde alrededor de 10mg/mL a alrededor de 250mg/mL; en donde la concentración del anticuerpo monoclonal es desde alrededor de 20mg/mL a alrededor de 40mg/mL; en donde la concentración del anticuerpo monoclonal es desde alrededor de 20mg/mL a alrededor de 250mg/mL; y, que comprende además un sacárido; en donde el sacárido es un disacárido.

1.3 En primera instancia, se debe advertir que algunas reivindicaciones se refieren al método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14: "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 15: "No serán patentables (...) c) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al método de tratamiento no sería patentable.

1.4. Al igual que, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: WO03105894 publicada el 24 de diciembre de 2003.

2.5. Ahora bien, el documento D1, particularmente en la descripción define una formulación líquida estabilizada de anticuerpos Anti-RSV. Particularmente, esta anterioridad D1 revela formulaciones líquidas de antígenos, las cuales exponen estabilidad, bajo los niveles imperceptibles de fragmentación del anticuerpo, bajo los niveles imperceptibles de agregación, y muy poco a ninguna pérdida de actividad biológica, aún durante o después de periodos largos de almacenaje. Según dicha anterioridad D1 en la página 21, líneas 2 y 3, se define una formulación farmacéutica estable que comprende un anticuerpo con un pH de 5.5 a 7.5, preferiblemente 5.5 en un búfer de histidina. Según esta anterioridad, la sal de histidina usada puede ser de acetato, tal y como lo evidencia en la página 20 línea 30, de dicho documento D1. Por lo tanto además que la presente solicitud comprende un método terapéutico no patentable a luz de la norma colombiana, también revela una formulación líquida de antígenos con el mismo pH en un amortiguador de acetato de histidina que no es novedoso como lo indica esta solicitud anterior D1 de 2003 que revela con anterioridad tal formulación. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo referido ya se encontraba en el estado de la técnica.

Por lo tanto, este documento objeto de oposición a la luz de documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 038.013 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- “Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita o oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 20 de octubre de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una formulación líquida de antígenos con el mismo pH en un amortiguador de acetato de histidina, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: “Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”. La presente solicitud carece de aplicación industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y la reivindicación no es objeto de patentabilidad pues es contrario a lo que dice la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- “Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMULACIÓN DE ANTICUERPO EN AMORTIGUADOR DE ACETATO DE HISTIDINA"**, cuyo titular es GENENTECH, INC, solicitada Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 599 del 31 de diciembre de 2008.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03105894 publicada el 24 de diciembre de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente. *X*
2. Documento que acredita al representante legal de PROCAPS S.A. *✓*
3. Recibo de caja del respectivo pago de tasa. *✓*
4. Copias de los documentos: *✓*

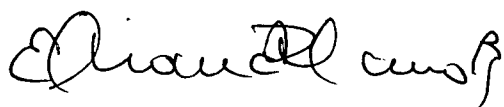
(sin poder)

c D1: WO03105894 publicada el 24 de diciembre de 2003.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

670 41-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CACA : 09 - 24,457
FECHA : MARZO 30 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-038013- -00004-0000

Fecha: 2009-03-30 14:14 50 Dep 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 100

***** CONSIGNACION *****

DT	TANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	vr. PAGO
LAB. PROCAPS		CONSIGNACION	BANCO DE BOGOTA	062754387	19814664	13/02/2009	170,000.00
LAB. PROCAPS		CONSIGNACION	BANCO DE BOGOTA	062754387	108513543	17/02/2009	170,000.00
LAB. PROCAPS		CONSIGNACION	BANCO DE BOGOTA	062754387	108516343	03/03/2009	2,565,000.00
LAB. PROCAPS		CONSIGNACION	BANCO DE BOGOTA	062754387	108516354	03/03/2009	170,000.00
LAB. PROCAPS		CONSIGNACION	BANCO DE BOGOTA	062754387	108530763	09/02/2009	452,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	287,000.00

SP CINCOCEIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CACA APLICADO AL EXPEDIENTE No. _____



***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente

***** C O N T I N U A *****

673
44



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. -----

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	

***** C O N T I N U A *****



***** Pag. 4
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, -----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----

***** C O N T I N U A *****

615 16



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, para que en nombre y representacion de PROCAPS ----
S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a
que este obligada la sociedad, en el giro normal de sus negocios y
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al señor MARLON ----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de ----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio ----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: EI representante legal de la -----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General -----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008,
otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente
se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008
bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento -----
publico Poder especial Amplio y Suficiente a la doctora MILENA ----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 19 de Marzo de 2008.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

m. Rojas

ANEXO 1

6 17 17

(32) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/105894 A1

(51) International Patent Classification⁷: A61K 39/385, 39/42, C07K 15/00

(74) Agents: INSOGNA, Anthony, M. et al; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(21) International Application Number: PCT/US03/18913

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 16 June 2003 (16.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/338,921 14 June 2002 (14.06.2002) US

(84) Designated States (*regional*): ARIPO patent (CH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, UJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): MED-IMMUNE, INC. [US/US]; 35 W. Watkins Mill Road, Gaithersburg, MD 20878 (US).

(72) Inventors; and

Published:

(75) Inventors/Applicants (*for US only*): OLIVER, Cynthia, N. [US/US]; 13517 Stonebarn Lane, N. Potomac, MD 20878 (US). SHANE, Erica [US/US]; 7254 Spring Side Way, McLean, VA 22101 (US). ISSAACS, Benjamin, S. [US/US]; Andover, MA (US). ALLAN, Christian, B. [US/US]; 4401 Gregg Road, Brookville, MD 20833 (US). CHANG, Stephen [US/US]; 329 Selwyn Dr., Apt. 3C, Frederick, MD 21701 (US).

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/105894 A1

(54) Title: STABILIZED LIQUID ANTI-RSV ANTIBODY FORMULATIONS

(57) Abstract: The present invention provides liquid formulations of SYNAGIS® or an antigenbinding fragment thereof that immunospecifically bind to a respiratory syncytial virus (RSV) antigen, which formulations exhibit stability, low to undetectable levels of aggregation, and very little to no loss of the biological activities of SYNAGIS® or an antigen binding fragment thereof, even during long periods of storage. In particular, the present invention provides liquid formulations of SYNAGIS® or an antigen binding fragment thereof which immunospecifically binds to a RSV antigen, which formulations are substantially free of surfactant, inorganic salts, and/or other common excipients. Furthermore, the invention provides method of preventing, treating or ameliorating symptoms associated with RSV infection utilizing liquid formulations of the present invention.

STABILIZED LIQUID ANTI-RSV ANTIBODY FORMULATIONS

This application is entitled to and claims priority benefit to U.S. provisional application Serial No. 60/388,921 filed June 14, 2002, which is incorporated herein by reference in its entirety.

1. INTRODUCTION

The present invention relates to liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, which formulations exhibit stability, low to undetectable levels of antibody fragmentation, low to undetectable levels of aggregation, and very little to no loss of the biological activity (*e.g.*, therapeutic efficacy) SYNAGIS® or an antigen-binding fragment thereof, even during or after long periods of storage. In particular, the present invention relates to liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, which formulations are substantially free of surfactant and/or inorganic salts. The present invention also relates to methods of preventing, treating or ameliorating symptoms associated with a respiratory syncytial virus (RSV) infection utilizing liquid formulations of SYNAGIS® or an antigen binding fragment thereof.

2. BACKGROUND OF THE INVENTION

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract disease in infants and children (Feigen *et al.*, eds., 1987, *In: Textbook of Pediatric Infectious Diseases*, WB Saunders, Philadelphia at pages 1653-1675; New Vaccine Development, Establishing Priorities, Vol. 1, 1985, National Academy Press, Washington DC at pages 397-409; and Ruuskanen *et al.*, 1993, *Curr. Probl. Pediatr.* 23:50-79). The yearly epidemic nature of RSV infection is evident worldwide, but the incidence and severity of RSV disease in a given season vary by region (Hall, C.B., 1993, *Contemp. Pediatr.* 10:92-110). In temperate regions of the northern hemisphere, it usually begins in late fall and ends in late spring (Hall, C.B., 1995, *In: Mandell G.L., Bennett J.E., Dolin R.*, eds., 1995, *Principles and Practice of Infectious Diseases*, 4th ed., Churchill Livingstone, New York at pages 1501-1519). It is estimated that RSV illness results in 90,000 hospitalizations and causes 4,500 deaths annually in the United States. Primary RSV infection occurs most often in children from 6 weeks to 2 years of age and uncommonly in

the first 4 weeks of life during nosocomial epidemics (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396). RSV is estimated to cause as much as 75% of all childhood bronchiolitis and up to 40% of all pediatric pneumonias (Cunningham, C.K. *et al.*, 1991, *Pediatrics* 88:527-532). Children at increased risk from RSV infection include preterm infants (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396) and children with bronchopulmonary dysplasia (Groothuis *et al.*, 1988, *Pediatrics* 82:199-203), congenital heart disease (MacDonald *et al.*, *New Engl. J. Med.* 307:397-400), congenital or acquired immunodeficiency (Ogra *et al.*, 1988, *Pediatr. Infect. Dis. J.* 7:246-249; and Pohl *et al.*, 1992, *J. Infect. Dis.* 165:166-169), and cystic fibrosis (Abman *et al.*, 1988, *J. Pediatr.* 113:826-830). The fatality rate in infants with heart or lung disease who are hospitalized with RSV infection is 3%-4% (Navas *et al.*, 1992, *J. Pediatr.* 121:348-354).

RSV infects adults as well as infants and children. In healthy adults, RSV causes predominantly upper respiratory tract disease. It has recently become evident that some adults, especially the elderly, have symptomatic RSV infections more frequently than had been previously reported (Evans, A.S., eds., 1989, *Viral Infections of Humans. Epidemiology and Control*, 3rd ed., Plenum Medical Book, New York at pages 525-544). Several epidemics also have been reported among nursing home patients and institutionalized young adults (Falsey, A.R., 1991, *Infect. Control Hosp. Epidemiol.* 12:602-608; and Garvie *et al.*, 1980, *Br. Med. J.* 281:1253-1254). Finally, RSV may cause serious disease in immunosuppressed persons, particularly bone marrow transplant patients (Hertz *et al.*, 1989, *Medicine* 68:269-281).

Treatment options for established RSV disease are limited. Severe RSV disease of the lower respiratory tract often requires considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields *et al.*, eds., 1990, *Fields Virology*, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072). The only drug approved for treatment of infection is the antiviral agent ribavirin (American Academy of Pediatrics Committee on Infectious Diseases, 1993, *Pediatrics* 92:501-504). It has been shown to be effective in the treatment of RSV pneumonia and bronchiolitis, modifying the course of severe RSV disease in immunocompetent children (Smith *et al.*, 1991, *New Engl. J. Med.* 325:24-29). However, ribavirin has a number of limitations including high cost, need for prolonged aerosol administration and potential risk to pregnant women as well as to exposed health care personnel. The American Academy of Pediatrics Committee on Infectious Diseases revised their recommendation for use of ribavirin. The current recommendation is that the decision to use ribavirin should be based on the particular

clinical circumstances and physician's experience (American Academy of Pediatrics.

Summaries of Infectious Diseases. In: Pickering L.K., ed., 2000 *Red Book: Report of the Committee on Infectious Diseases*. 25th ed., Elk Grove Village, IL, American Academy of Pediatrics, 2000, pp. 483-487).

- 5 While a vaccine might prevent RSV infection, no vaccine is yet licensed for this indication. A major obstacle to vaccine development is safety. A formalin-inactivated vaccine, though immunogenic, unexpectedly caused a higher and more severe incidence of lower respiratory tract disease due to RSV in immunized infants than in infants immunized with a similarly prepared trivalent parainfluenza vaccine (Kim *et al.*, 1969, *Am. J.*
- 10 *Epidemiol.* 89:422-434; and Kapikian *et al.*, 1969, *Am. J. Epidemiol.* 89:405-421). Several candidate RSV vaccines have been abandoned and others are under development (Murphy *et al.*, 1994, *Virus Res.* 32:13-36), but even if safety issues are resolved, vaccine efficacy must also be improved. A number of problems remain to be solved. Immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory
- 15 tract disease occurs at 2-5 months of age. The immaturity of the neonatal immune response together with high titers of maternally acquired RSV antibody may be expected to reduce vaccine immunogenicity in the neonatal period (Murphy *et al.*, 1988, *J. Virol.* 62:3907-3910; and Murphy *et al.*, 1991, *Vaccine* 9:185-189). Finally, primary RSV infection and disease do not protect well against subsequent RSV disease (Henderson *et al.*, 1979, *New*
- 20 *Engl. J. Med.* 300:530-534).

Currently, the only approved approach to prophylaxis of RSV disease is passive immunization. Initial evidence suggesting a protective role for IgG was obtained from observations involving maternal antibody in ferrets (Prince, G.A., Ph.D. diss., University of California, Los Angeles, 1975) and humans (Lambrecht *et al.*, 1976, *J. Infect. Dis.* 134:211-

25 217; and Glezen *et al.*, 1981, *J. Pediatr.* 98:708-715). Hemming *et al.* (Morell *et al.*, eds., 1985, *Clinical Use of Intravenous Immunoglobulins*, Academic Press, London at pages 289-294) recognized the possible utility of RSV antibody in the treatment or prevention of RSV infection during studies involving the pharmacokinetics of an intravenous immune globulin (IVIG) in newborns suspected of having neonatal sepsis. They noted that one infant, whose

30 respiratory secretions yielded RSV, recovered rapidly after IVIG infusion. Subsequent analysis of the IVIG lot revealed an unusually high titer of RSV neutralizing antibody. This same group of investigators then examined the ability of hyperimmune serum or immune globulin, enriched for RSV neutralizing antibody, to protect cotton rats and primates against RSV infection (Prince *et al.*, 1985, *Virus Res.* 3:193-206; Prince *et al.*, 1990, *J. Virol.*

WO 03/105894

PCT/US03/18913

64:3091-3092; Hemming *et al.*, 1985, *J. Infect. Dis.* 152:1083-1087; Prince *et al.*, 1983, *Infect. Immun.* 42:81-87; and Prince *et al.*, 1985, *J. Virol.* 55:517-520). Results of these studies suggested that RSV neutralizing antibody given prophylactically inhibited respiratory tract replication of RSV in cotton rats. When given therapeutically, RSV antibody reduced pulmonary viral replication both in cotton rats and in a nonhuman primate model. Furthermore, passive infusion of immune serum or immune globulin did not produce enhanced pulmonary pathology in cotton rats subsequently challenged with RSV.

A humanized antibody directed to an epitope in the A antigenic site of the F protein of RSV, SYNAGIS[®], comprising variable heavy (VH) complementarity determining regions (CDRs) having the amino acid sequences of SEQ ID NO:1-3 and variable light (VL) CDRs having the amino acid sequences of SEQ ID NO:4-6, is approved for intramuscular administration to pediatric patients for prevention of serious lower respiratory tract disease caused by RSV at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere).

SYNAGIS[®] is a composite of human (95%) and murine (5%) antibody sequences. See, Johnson *et al.*, 1997, *J. Infect. Diseases* 176:1215-1224 and U.S. Patent No. 5,824,307, the entire contents of which are incorporated herein by reference. The human heavy chain sequence was derived from the constant domains of human IgG₁ and the variable framework regions of the VH genes of Cor (Press *et al.*, 1970, *Biochem. J.* 117:641-660) and Cess (Takashi *et al.*, 1984, *Proc. Natl. Acad. Sci. USA* 81:194-198). The human light chain sequence was derived from the constant domain of C6 and the variable framework regions of the VL gene K104 with J6-4 (Bentley *et al.*, 1980, *Nature* 288:5194-5198). The murine sequences were derived from a murine monoclonal antibody, Mab 1120 (Beeler *et al.*, 1989, *J. Virology* 63:2941-2950), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks.

SYNAGIS[®] has high specific activity against RSV *in vitro* (approximately 50-100 times that of RespiGam[®]) and is known to neutralize a broad range of RSV isolates. Since it is not derived from human plasma, prophylactic treatment with SYNAGIS[®] does not carry potential risk of transmission of blood borne pathogens.

SYNAGIS[®] was initially formulated as a liquid for IV use, at a concentration of 10 mg/ml SYNAGIS[®] in phosphate buffered saline. A lyophilized formulation of SYNAGIS[®], which allows a higher concentration (100 mg/ml after reconstitution, in 50 mM histidine and 3.2 mM glycine buffer with 6% (w/v) mannitol at pH 6.0) of the antibody than this initial liquid formulation, was produced later to allow intramuscular use. The lyophilizer,

6222

formulation of SYNAGIS® is prepared by lyophilizing SYNAGIS® at 54 mg/ml in an aqueous solution containing 25 mM histidine, 1.6 mM glycine, and 3% (w/v) mannitol at pH 6.0. The initial liquid formulation in PBS and the lyophilized formulation of SYNAGIS® have been tested in phase I clinical studies in healthy adults. The lyophilized formulation was tested in phase I through phase IV studies in pediatric patients. SYNAGIS®, at doses of 15 mg/kg to 30 mg/kg for adults is found to be well tolerated, and 15 mg/kg for children is found to be safe and efficacious for RSV prophylaxis. The lyophilized formulation was approved in 1998 by the FDA for use in the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

However, the lyophilized formulation has a number of limitations, including a prolonged process for lyophilization and resulting high cost for manufacturing. In addition, the lyophilized formulation has to be reconstituted aseptically and accurately by healthcare practitioners prior to administering to patients. The reconstitution step itself requires certain specific procedures: (1) a sterile diluent (i.e., water or 5% dextrose in water for intravenous administration and water for intramuscular administration) is added to the vial containing lyophilized SYNAGIS®, slowly and aseptically, and the vial must be swirled very gently for 30 seconds to avoid foaming; (2) the reconstituted SYNAGIS® needs to stand at room temperature for a minimum of 20 minutes until the solution clarifies; and (3) the reconstituted preparation must be administered within six (6) hours after the reconstitution. Such reconstitution procedure is cumbersome and the time limitation after the reconstitution can cause a great inconvenience in administering the formulation to patients, leading to significant waste, if not reconstituted properly or if the reconstituted dose is not used within six (6) hours and must be discarded.

Thus, a need exists for a liquid formulation of SYNAGIS® at a concentration comparable to or higher than the reconstituted lyophilized formulation so that there is no need to reconstitute the formulation prior to administration. This allows healthcare practitioners much quicker and easier administration of SYNAGIS® to a patient.

Prior liquid antibody preparations have short shelf lives and may lose biological activity of the antibodies resulting from chemical and physical instabilities during the storage. Chemical instability may be caused by deamidation, racemization, hydrolysis, oxidation, beta elimination or disulfide exchange, and physical instability may be caused by antibody denaturation, aggregation, precipitation or adsorption. Among these, aggregation, deamidation and oxidation are known to be the most common causes of the antibody

degradation (Wang *et al.*, 1988, *J. of Parenteral Science & Technology* 42(Suppl):S4-S26; Cleland *et al.*, 1993, *Critical Reviews in Therapeutic Drug Carrier Systems* 10(4):307-377).

Thus, there is a need for a stable liquid formulation of SYNAGIS® or an antigen-binding fragment thereof effective to prevent RSV infection.

5

3. SUMMARY OF INVENTION

The present invention is based, in part, on the development of high concentration liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, which formulations exhibit, in the absence of surfactant, inorganic salts, and/or other excipients, stability, low to undetectable levels of antibody fragmentation and/or aggregation, and very little to no loss of the biological activity(ies) of SYNAGIS® or an antigen-binding fragment thereof during manufacture, preparation, transportation, and storage. The liquid formulations of the present invention facilitate the administration of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management and/or amelioration of a RSV infection or one or more symptoms thereof. In particular, the liquid formulations of the present invention enable a healthcare professional to quickly administer a sterile dosage of SYNAGIS® or an antigen-binding fragment thereof without having to accurately and aseptically reconstitute the antibody or antibody fragment prior to administration as required for the lyophilized dosage form. Such liquid formulations of SYNAGIS® can be also manufactured more easily and cost effectively than the lyophilized formulation since liquid formulations do not require a prolonged drying step, such as lyophilization, freeze-drying, etc. The liquid formulations are made by a process in which the antibody being formulated is in an aqueous phase throughout the purification and formulation process. Preferably, the liquid formulations are made by a process that does not include a drying step, for example, but not by way of limitation, a lyophilization, freeze-drying, spray-drying, or air-drying step.

The present invention provides liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, substantially free of surfactant, inorganic salts, sugars, and/or other common excipients, said formulations comprising histidine and a concentration of about 15 mg/ml or higher of SYNAGIS® or an antigen-binding fragment thereof. Optionally, the formulation may further comprise glycine. Alternatively, the formulation of the present invention may further comprise other common excipients, such as ~~saccharides~~ polyols and amino acids, including, but not limited to, arginine, lysine, and methionine. The present invention also provides liquid formulations substantially free of surfactant,

inorganic salts, sugars, and/or other commonly-known excipients, said formulation having a pH ranging from about 5.0 to about 7.0, preferably about 5.5 to 6.5, more preferably about 5.8 to about 6.2, and most preferably about 6.0, and comprising histidine and a concentration of about 15 mg/ml or higher of SYNAGIS® or an antigen-binding fragment thereof.

The present invention encompasses stable liquid formulations of SYNAGIS® which exhibit low to undetectable levels of antibody aggregation and/or fragmentation with very little to no loss of biological activity(ies) of SYNAGIS® or an antigen-binding fragment thereof during manufacture, preparation, transportation and long periods of storage. The present invention also encompasses stable liquid formulations of modified forms of SYNAGIS® or an antigen-binding fragment thereof that have increased *in vivo* half-lives relative to unmodified SYNAGIS® or an antigen-binding fragment thereof, said formulations exhibiting low to undetectable levels of antibody aggregation and/or fragmentation, and very little to no loss of biological activity(ies) of SYNAGIS® or an antigen-binding fragment thereof.

The present invention encompasses liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, said formulations having stability at 38° - 42°C as assessed by high performance size exclusion chromatography (HPSEC). The liquid formulations of the present invention exhibit stability, as assessed by HPSEC, at the temperature ranges of 38°C-42°C for at least 60 days (in specific embodiments, not more than 120 days), of 20°C-24°C for at least 1 year, and of 2°C-8°C for at least 3 years. The present invention also encompasses liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, said formulations having low to undetectable aggregation as measured by HPSEC. In a preferred embodiment, the liquid formulations of the present invention exhibit stability at 38°-42°C for at least 60 days and exhibit low to undetectable levels of antibody aggregation as measured by HPSEC, and further, exhibit very little to no loss of biological activity (ies) of SYNAGIS® or an antigen-binding fragment thereof compared to the reference antibodies as measured by antibody binding assays such as, e.g., ELISAs.

The present invention provides methods for preparing liquid formulations of SYNAGIS® or an antigen-binding fragment thereof. The liquid formulations of the present invention are prepared by maintaining SYNAGIS® or an antigen-binding fragment thereof in an aqueous solution at any time during the preparation. In other words, the liquid formulations are prepared without involving any step of drying SYNAGIS® or an antigen-

binding fragment thereof or the formulations themselves by, for example, lyophilization, vacuum drying, etc.

The present invention provides methods for preparing liquid formulations of SYNAGIS® or an antigen-binding fragment thereof, said methods comprising concentrating
5 a fraction of purified SYNAGIS® or an antigen-binding fragment thereof to a final concentration of about 15 mg/ml, about 20 mg/ml, about 30 mg/ml, about 40 mg/ml, about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 200 mg/ml, about 250 mg/ml, or about 300 mg/ml using a semi-permeable membrane with an appropriate molecular weight (mw) cutoff (e.g., 30 kD cutoff for
10 SYNAGIS® and F(ab')₂ fragments thereof; and 10 kD cutoff for SYNAGIS® fragments such Fab fragments), and diafiltering the concentrated antibody fraction into the formulation buffer using the same membrane. The formulation buffer of the present invention comprises histidine at a concentration ranging from about 1 mM to about 100 mM, about 10 mM to about 50 mM, about 20 mM to about 30 mM, or about 23 mM to about 27 mM, and
15 is most preferably about 25 mM. To obtain an appropriate pH for SYNAGIS® or an antigen-binding fragment thereof, it is preferably that histidine (and glycine, if added) is first dissolved in water to obtain a buffer solution with higher pH than the desired pH and then the pH is brought down to the desired level by the addition of HCl. This way, the formation of inorganic salts (e.g., the formation of NaCl when, e.g., histidine hydrochloride
20 is used as the source of histidine and the pH is raised to the desired level by the addition of NaOH) can be avoided.

The liquid formulations of the present invention may be sterilized by sterile filtration using a 0.2 µ or a 0.22 µ filter. Sterilized liquid formulations of the present invention may be administered to a subject to prevent, treat or ameliorate one or more symptoms
25 associated with a RSV infection or a symptom thereof.

The present invention also provides kits comprising the liquid formulations of SYNAGIS® or an antigen-binding fragment thereof for use by, e.g. a healthcare professional. The present invention further provides methods of preventing, treating managing or ameliorating a RSV infection or one or more symptoms thereof by
30 administering the liquid formulations of the present invention.

3.1 Terminology

As used herein, all liquid formulations of SYNAGIS® and/or fragments thereof that immunospecifically bind to a RSV antigen described above are collectively referred to as

"liquid formulations of the invention," "SYNAGIS[®] liquid formulations of the invention," or "liquid formulations of SYNAGIS[®] or an antigen-binding fragment thereof."

As used herein, the term "cytokine receptor modulator" refers to an agent which modulates the phosphorylation of a cytokine receptor, the activation of a signal transduction pathway associated with a cytokine receptor, and/or the expression of a particular protein such as a cytokine. Such an agent may directly or indirectly modulate the phosphorylation of a cytokine receptor, the activation of a signal transduction pathway associated with a cytokine receptor, and/or the expression of a particular protein such as a cytokine. Thus, examples of cytokine receptor modulators include, but are not limited to, cytokines, fragments of cytokines, fusion proteins and antibodies that immunospecifically binds to a cytokine receptor or a fragment thereof. Further, examples of cytokine receptor modulators include, but are not limited to, peptides, polypeptides (e.g., soluble cytokine receptors), fusion proteins and antibodies that immunospecifically binds to a cytokine or a fragment thereof.

As used herein, the terms "SYNAGIS[®] fragment", "antigen-binding fragment" and like terms used in the context of SYNAGIS[®] refer to a fragment of SYNAGIS[®] that immunospecifically binds to a RSV antigen. Fragments of SYNAGIS[®] may be generated by any technique known to those skilled in the art. For example, Fab and F(ab')₂ fragments may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the complete light chain, and the variable region, the CH1 region and the hinge region of the heavy chain. Preferably, the fragment also binds to a RSV antigen, more preferably to the same epitope as SYNAGIS[®].

As used herein, the term "effective amount" refers to the amount of a therapy (e.g., a prophylactic or therapeutic agent), which is sufficient to reduce the severity, and/or duration of a RSV infection, ameliorate one or more symptoms thereof, prevent the advancement of a RSV infection, or cause regression of a RSV infection, or which is sufficient to result in the prevention of the development, recurrence, onset, or progression of a RSV infection or one or more symptoms thereof, or enhance or improve the prophylactic and/or therapeutic effect(s) of another therapy (e.g., another therapeutic agent). In a specific embodiment, an effective amount of a therapeutic or a prophylactic agent reduces one or more of the following steps of a RSV life cycle: the docking of the virus particle to a cell, the introduction of viral genetic information into a cell, the expression of viral proteins, the production of new virus particles and the release of virus particles from a cell by at least

WO 03/105894

PCY/US03/18913

5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%. In another specific embodiment, an effective amount of a therapeutic or a

5 prophylactic agent reduces the replication, multiplication or spread of a virus by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

As used herein, the term "epitope" refers to a portion of a RSV polypeptide or
10 protein having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. An epitope having immunogenic activity is a portion of a RSV polypeptide or protein that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a RSV polypeptide or protein to which an antibody immunospecifically binds as determined by any method well known in the art, for example,
15 by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic. Specifically, the epitope of SYNAGIS® is the A antigenic site of the F protein of RSV.

As used herein, the term "excipients" refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes,
20 but not limited to, proteins (*e.g.*, serum albumin, etc.), amino acids (*e.g.*, aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (*e.g.*, alkyl sulfonates, caprylate, etc.), surfactants (*e.g.*, SDS, polysorbate, nonionic surfactant, etc.), saccharides (*e.g.*, sucrose, maltose, trehalose, etc.) and polyols (*e.g.*, mannitol, sorbitol, etc.). Also see Remington's Pharmaceutical Sciences (by Joseph P. Remington,
25 18th ed., Mack Publishing Co., Easton, PA) which is hereby incorporated in its entirety. Preferably, the excipients impart a beneficial physical property to the formulation, such as increased protein stability, increased protein solubility and decreased viscosity.

The term "fragment" as used herein refers to a peptide, polypeptide, or protein (including an antibody) comprising an amino acid sequence of at least 5 contiguous amino
30 acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least contiguous 80 amino acid residues, at least contiguous 90 amino acid residues, at

least contiguous 100 amino acid residues, at least contiguous 125 amino acid residues, at least 150 contiguous amino acid residues, at least contiguous 175 amino acid residues, at least contiguous 200 amino acid residues, or at least contiguous 250 amino acid residues of the amino acid sequence of another polypeptide or protein. In a specific embodiment, a
5 fragment of a protein or polypeptide retains at least one function of the protein or polypeptide. In another embodiment, a fragment of a protein or polypeptide retains at least two, three or four functions of the protein or polypeptide. Preferably a fragment of an antibody that immunospecifically binds to a RSV antigen retains the ability to bind to a RSV antigen.

10 As used herein, the term "fusion protein" refers to a polypeptide or protein that comprises an amino acid sequence of a first protein, polypeptide or fragment, analog or derivative thereof, and an amino acid sequence of a heterologous protein or polypeptide (i.e., a second protein, polypeptide or fragment, analog or derivative thereof different than the first protein or functional fragment, analog or derivative thereof). In one embodiment, a
15 fusion protein comprises a prophylactic or therapeutic agent fused to a heterologous protein, polypeptide or peptide. In accordance with this embodiment, the heterologous protein, polypeptide or peptide may or may not be a different type of prophylactic or therapeutic agent.

As used herein, the term "human infant" refers to a human less than 24 months, preferably less than 16 months, less than 12 months, less than 6 months, less than 3 months, less than 2 months, or less than 1 month of age.

As used herein, the term "human infant born prematurely" refers to a human born at less than 40 weeks gestational age, preferably less than 35 weeks gestational age, who is less than 6 months old, preferably less than 3 months old, more preferably less than 2
25 months old, and most preferably less than 1 month old.

As used herein, the term "high concentration" refers to a concentration of 50 mg/ml or higher, preferably 95 mg/ml or higher of an antibody or fragment thereof that immunospecifically binds to a RSV antigen, in an antibody formulation.

As used herein, the term "host cell" includes a subject cell transfected or
30 transformed with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

As used herein, the term "immunospecifically binds a RSV antigen" and analogous terms refer to antibodies or fragments thereof that specifically bind to a RSV antigen thereof and do not specifically bind to other polypeptides. Antibodies or fragments that immunospecifically bind a RSV antigen may be cross-reactive with related antigens.

- 5 Preferably, antibodies or fragments that immunospecifically bind a RSV antigen do not cross-react with other antigens. Antibodies or fragments that immunospecifically bind to and RSV antigen can be identified, for example, by immunoassays, ELISA, isothermal titration calorimetry, or other techniques known to those of skilled in the art. An antibody or an antigen-binding fragment thereof binds specifically to a RSV antigen when it binds
10 with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). See, e.g., Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

- The term "in combination" as used herein refers to the use of more than one
15 therapies (e.g., prophylactic and/or therapeutic agents). The use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a RSV infection. A first therapy (e.g., a prophylactic or therapeutic agent) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48
20 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to a subject with a RSV infection.
25

- As used herein, the term "inorganic salt" refers to any compounds, containing no carbon, that result from replacement of part or all of the acid hydrogen or an acid by a metal or a group acting like a metal and are often used as a tonicity adjusting compound in pharmaceutical compositions and preparations of biological materials. The most common
30 inorganic salts are NaCl, KCl, NaH_2PO_4 , etc.

An "isolated" or "purified" antibody is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody

WO 03/105894

PCT/US03/18913

in which the polypeptide/protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of the antibody having less than about 30%, 20%, 10%, 5%, 2.5%, or 1%, (by dry weight) of contaminating protein. When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When antibody is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than antibody of interest. In a preferred embodiment of the present invention, antibodies are isolated or purified.

As used herein, the phrase "low to undetectable levels of aggregation" refers to samples containing no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, and most preferably no more than 0.5%, aggregation by weight protein as measured by high performance size exclusion chromatography (HPSEC).

As used herein, the term "low to undetectable levels of fragmentation" refers to samples containing equal to or more than 80%, 85%, 90%, 95%, 98%, or 99%, of the total protein, for example, in a single peak as determined by high performance size exclusion chromatography (HPSEC), or in two (2) peaks (heavy- and light-chains) by reduced Capillary Gel Electrophoresis (rCGE), representing the non-degraded SYNAGIS[®] or a non-degraded fragment thereof which immunospecifically binds to a RSV antigen, and containing no other single peaks having more than 5%, more than 4%, more than 3%, more than 2%, more than 1%, or more than 0.5% of the total protein each. The term "Reduced-Capillary Gel Electrophoresis (CGE)" as used herein refers to capillary gel electrophoresis under reducing conditions sufficient to reduce disulfide bonds in SYNAGIS[®] or an antigen-binding fragment thereof.

As used herein, the terms "manage", "managing" and "management" refer to the beneficial effects that a subject derives from a therapy (*e.g.*, SYNAGIS[®] or an antigen-binding fragment thereof), which does not result in a cure of a RSV infection. In certain embodiments, a subject is administered one or more therapies (*e.g.*, prophylactic or therapeutic agents) to "manage" a RSV infection or a symptom thereof so as to prevent the progression or worsening of the infection.

As used herein, the term "modified" in the context of modified forms of SYNAGIS® or an antigen-binding fragment thereof refers to SYNAGIS® or an antigen-binding fragment thereof which has been altered by any method known in the art to increase its half life (see, e.g., Section 5.1.1., *infra*). SYNAGIS® and antigen-binding fragments thereof with improved *in vivo* half-lives and methods for preparing them are disclosed in International Publication No. WO 02/060919, filed December 12, 2001, and U.S. Patent Application No. 10/020,354, filed December 12, 2001, both entitled "Molecules with Extended Half-Lives, Compositions and Uses" and by L. Johnson *et al.* which are hereby incorporated by reference in their entireties. The term "modified" in the context of SYNAGIS® or an antigen-binding fragment thereof also refers to SYNAGIS® or an antigen-binding fragment modified by covalent attachment of any type of molecule to SYNAGIS® or an antigen-binding fragment thereof. For example, but not by way of limitation, SYNAGIS® or an antigen-binding fragment thereof may be modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc.

As used herein, the term "pharmaceutically acceptable" means being approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopia, European Pharmacopia or other generally recognized pharmacopia for use in animals, and more particularly in humans.

As used herein, the term "polyol" refers to a sugar that contains many -OH groups compared to a normal saccharide.

As used herein, the terms "prevent", "preventing", and "prevention" refer to the prevention or reduction of the recurrence, onset, development or progression of a RSV infection, or the prevention or reduction of the severity and/or duration of a RSV infection or one or more symptoms thereof.

As used herein, the terms "prophylactic agent" and "prophylactic agents" refer to any agent(s) which can be used in the prevention of a RSV infection or one or more symptoms thereof. In certain embodiments, the term "prophylactic agent" refers to SYNAGIS® or an antigen-binding fragment thereof. In accordance with these embodiments, the antibody or antibody fragment may be a component of a liquid formulation of the invention. In certain other embodiments, the term "prophylactic agent" does not refer to SYNAGIS® or an antigen-binding fragment thereof. In yet other embodiments, the term "prophylactic agent" does not refer to antibodies or fragments thereof other than SYNAGIS® that immunospecifically bind to a RSV antigen. Preferably,

a prophylactic agent is an agent which is known to be useful to, or has been or is currently being used to prevent or impede the onset, development, progression, and/or severity of a RSV infection or a symptom thereof.

As used herein, the term "prophylactically effective amount" refers to the amount of a liquid formulation of the invention which is sufficient to result in the prevention of the development, recurrence, onset or progression of a RSV infection. In a specific embodiment, a prophylactically effective amount of a prophylactic agent reduces one or more of the following steps of a RSV life cycle: the docking of the virus particle to a cell, the introduction of viral genetic information into a cell, the expression of viral proteins, the production of new virus particles and the release of virus particles from a cell by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%. In another specific embodiment, a prophylactically effective amount of a prophylactic agent reduces the replication, multiplication or spread of a virus by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

As used herein, the term "RSV antigen" refers to a RSV protein, polypeptide or peptide to which an antibody immunospecifically binds.

As used herein, the term "saccharide" refers to a class of molecules that are polyhydric alcohols. Saccharides are commonly referred to as carbohydrates and may contain different amounts of sugar (saccharide) units, e.g., monosaccharides, disaccharides and polysaccharides.

The term "small molecule" and analogous terms include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogues, polynucleotides, polynucleotide analogues, nucleotides, nucleotide analogues, organic or inorganic compounds (*i.e.*, including heterorganic and/or organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

As used herein, The terms "stability" and "stable" in the context of a liquid formulation comprising SYNAGIS® or an antigen-binding fragment thereof refer to the resistance of SYNAGIS® or an antigen-binding fragment thereof in the formulation to thermal and chemical unfolding, aggregation, degradation or fragmentation under given manufacture, preparation, transportation and storage conditions. The "stable" formulations of the invention retain biological activity equal to or more than 80%, 85%, 90%, 95%, 98%, 99%, or 99.5% under given manufacture, preparation, transportation and storage conditions. The stability of SYNAGIS® or an antigen-binding fragment thereof can be assessed by degrees of aggregation, degradation or fragmentation by methods known to those skilled in the art, including but not limited to reduced Capillary Gel Electrophoresis (rCGE), Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and HPSEC, compared to a reference, that is, a commercially available lyophilized SYNAGIS® reconstituted to 100 mg/ml in 47 mM histidine/3 mM glycine buffer with 5.6% mannitol at pH 5.0. The reference regularly gives a single peak ($\geq 97\%$ area) by HPSEC. The overall stability of a liquid formulation comprising SYNAGIS® or an antigen-binding fragment thereof that immunospecifically binds to a RSV antigen can be assessed by various immunological assays including, for example, ELISA and radioimmunoassay using the specific epitope of RSV.

As used herein, the term "SYNAGIS® standard reference" or analogous terms refer to commercially available lyophilized SYNAGIS®, as described in the Physicians' Desk Reference, 56th edition, 2002. Reconstituted SYNAGIS® may contain, e.g., the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% manitol and the active ingredient, the antibody, at a concentration of 100 milligrams per ml solution.

The terms "subject" and "patient" are used interchangeably herein. As used herein, the terms "subject" and "subjects" refer to an animal, preferably a mammal including a non-primate (e.g., a cow, pig, horse, cat, dog, rat, and mouse) and a primate (e.g., a chimpanzee, a monkey such as a cynomolgous monkey, and a human), and more preferably a human.

As used herein, the term "substantially free of surfactant" refers to a formulation of SYNAGIS® or an antigen-binding fragment thereof, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactant.

As used herein, the term "substantially free of inorganic salts" refers to a formulation of SYNAGIS® or an antigen-binding fragment thereof, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

As used herein, the term "surfactant" refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment, management or amelioration a RSV infection or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" refers to SYNAGIS® or an antigen-binding fragment thereof. In accordance with these embodiments, the antibody or antibody fragment may be a component of a liquid formulation of the invention. In certain other embodiments, the term "therapeutic agent" does not refer to SYNAGIS® or an antigen-binding fragment thereof. In yet other embodiments, the term "therapeutic agent" does not refer to antibodies or fragments thereof, other than SYNAGIS® that immunospecifically bind to a RSV antigen. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management or amelioration of a RSV infection or one or more symptoms thereof.

As used herein, the term "therapeutically effective amount" refers to the amount of a liquid formulation of the invention that reduces or ameliorates the progression, severity, and/or duration of a RSV infection, and/or ameliorates one or more symptoms associated with a RSV infection. With respect to the treatment of a RSV infection, a therapeutically effective amount refers to the amount of a therapeutic agent sufficient to reduce or inhibit the replication of a virus, inhibit or reduce the infection of cell with the virus, inhibit or reduce the production of the viral particles, inhibit or reduce the release of viral particles, inhibit or reduce the spread of the virus to other tissues or subjects, or ameliorate one or more symptoms associated with the infection. In a specific embodiment, a therapeutically effective amount of a therapeutic agent reduces one or more of the following steps of a RSV life cycle: the docking of the virus particle to a cell, the introduction of viral genetic information into a cell, the expression of viral proteins, the production of new virus particles and the release of virus particles from a cell by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%,

at least 85%, at least 90%, at least 95%, or at least 100%. In another specific embodiment, a therapeutically effective amount of a therapeutic agent reduces the replication, multiplication or spread of a virus by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

As used herein, the terms "therapies" and "therapy" can refer to any protocol(s), method(s) and/or agent(s) that can be used in the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to biological therapy, and/or other therapies useful for the treatment of a RSV infection known to medical personnel skilled.

As used herein, the terms "treat", "treating" and "treatment" refer to the reduction or amelioration of the progression, severity, and/or duration of a RSV infection and/or reduces or ameliorates one or more symptoms of a RSV infection. In specific embodiments, such terms refer to the reduction or inhibition of the replication of a respiratory syncytial virus (RSV), the inhibition or reduction in the spread of a respiratory syncytial virus (RSV) to other tissues or subjects, the inhibition or reduction of infection of a cell with a respiratory syncytial virus (RSV), or the amelioration of one or more symptoms associated with a respiratory syncytial virus (RSV) infection.

As used herein, a "protocol" includes dosing schedules and dosing regimens. The protocols herein are methods of use and include prophylactic and therapeutic protocols.

As used herein, the term "T cell receptor modulator" refers to an agent which modulates the phosphorylation of a T cell receptor, the activation of a signal transduction pathway associated with a T cell receptor and/or the expression of a particular protein such as a cytokine. Such an agent may directly or indirectly modulate the phosphorylation of a T cell receptor, the activation of a signal transduction pathway associated with a T cell receptor, and/or the expression of a particular protein such as a cytokine. Examples of T cell receptor modulators include, but are not limited to, peptides, polypeptides, proteins, fusion proteins and antibodies which immunospecifically bind to a T cell receptor or a fragment thereof. Further, examples of T cell receptor modulators include, but are not limited to, proteins, peptides, polypeptides (e.g., soluble T cell receptors), fusion proteins and antibodies that immunospecifically binds to a ligand for a T cell receptor or a fragment thereof.

As used herein, the term "very little to no loss of the biological activities" refers to antibody activities, including specific binding abilities of SYNAGIS® or an antigen-binding fragment as measured by various immunological assays, including, but not limited to ELISAs and radioimmunoassays. In one embodiment, SYNAGIS® or an antigen-binding
5 fragment of the liquid formulations of the invention retain approximately 50%, preferably 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98% of the ability to immunospecifically bind to a RSV antigen as compared to a reference antibody or antibody fragment as measured by an immunological assay known to one of skill in the art or described herein. For example, an ELISA based assay may be used to compare the ability
10 of a liquid formulation of SYNAGIS® or an antigen-binding fragment thereof to immunospecifically bind to a RSV antigen to a SYNAGIS® reference standard. In this assay, plates are coated with a RSV antigen and the binding signal of a set concentration of a SYNAGIS® reference standard is compared to the binding signal of the same concentration of a test antibody or antibody fragment.

15

4. BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a schematic diagram showing the outline for preparing purified SYNAGIS®.

Fig. 2 shows the clinical study flow chart for comparing the liquid formulation of SYNAGIS® with the lyophilized formulation of SYNAGIS®.

20

5. DETAILED DESCRIPTION OF THE INVENTION

The liquid formulations of the present invention provide a ready-to-use preparation of SYNAGIS® or an antigen-binding fragment thereof for administering to a subject without having to reconstitute the preparation accurately and aseptically and waiting for a period of time until the solution clarifies before administering the formulation to the subject. It
25 simplifies the procedure of administering the formulation to a subject for a healthcare professional. Furthermore, due to its high stability during the storage, the formulations of the present invention can contain SYNAGIS® or an antigen-binding fragment thereof at concentrations in the range of about 15 mg/ml to about 300 mg/ml without causing an adverse effect on the biological activity(ies) of SYNAGIS® or an antigen-binding fragment
30 thereof due to protein aggregation and/or fragmentation during a prolonged storage. Such stability not only ensures the efficacy of SYNAGIS® or an antigen-binding fragment thereof but also reduces possible risks of causing adverse effects on a subject. In addition, the manufacturing process of the liquid formulations of the present invention is simplified and

more efficient than the manufacturing process for the lyophilized version because all stages of the manufacturing of the liquid formulations are carried out in an aqueous solution, involving no drying process, such as lyophilization and freeze-drying. Accordingly, it is more cost effective as well.

5.1 SYNAGIS® Liquid Formulations

The liquid formulations of the present invention provide antibody formulations which are substantially free of surfactant, inorganic salts, and/or other excipients and yet exhibit high stability during long periods of storage. In a specific embodiment, such antibody formulations are homogeneous. The formulations of the present invention
10 comprise histidine at concentrations between 1 and 100 mM and SYNAGIS® or an antigen-binding fragment thereof at concentrations of about 15 mg/ml to about 300 mg/ml. In one embodiment, the formulations of the invention do not comprise other ingredients except for water or suitable solvents. In another specific embodiment, a modified form of SYNAGIS®
15 antibody or an antigen-binding fragment thereof having improved half-life and/or affinity is used in the liquid formulations of the invention.

The concentration of SYNAGIS® or an antigen-binding fragment thereof which is included in the liquid formulations of the invention, is at least 15 mg/ml, at least 20 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 35 mg/ml, at least 40 mg/ml, at least 45 mg/ml, at least 50 mg/ml, at least 55 mg/ml, at least 60 mg/ml, at least 65 mg/ml, at least 70 mg/ml,
20 at least 75 mg/ml, at least 80 mg/ml, at least 85 mg/ml, at least 90 mg/ml, at least 95 mg/ml, at least 100 mg/ml, at least 105 mg/ml, at least 110 mg/ml, at least 115 mg/ml, at least 120 mg/ml, at least 125 mg/ml, at least 130 mg/ml, at least 135 mg/ml, at least 140 mg/ml, at least 150 mg/ml, at least 200 mg/ml, at least 250 mg/ml, or at least 300 mg/ml.

The concentration of histidine which is included in the liquid formulations of the
25 invention ranges from about 1 mM to about 100 mM, about 10 mM to about 50 mM, about 20 mM to about 30 mM, or about 23 mM to about 27 mM, and is most preferably about 25 mM. Histidine can be in the form of L-histidine, D-histidine, or a mixture thereof, but L-histidine is the most preferable. Histidine can be also in the form of hydrates. Histidine may be used in a form of pharmaceutically acceptable salt, such as hydrochloride (e.g.,
30 monohydrochloride and dihydrochloride), hydrobromide, sulfate, acetate, etc. The purity of histidine should be at least 98%, preferably at least 99%, and most preferably at least 99.5%.

The pH of the formulation should not be equal to the isoelectric point of the particular antibody to be used in the formulation (e.g., the isoelectric point of SYNAGIS® ranges from 8.65 to 9.43) and may range from about 5.0 to about 7, preferably about 5.5 to about 6.5, more preferably about 5.8 to about 6.2, and most preferably about 6.0.

5 In addition to histidine and SYNAGIS® or an antigen-binding fragment thereof, the formulations of the present invention may further comprise glycine at a concentration of less than 150 mM, less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.8 mM, and most preferably 1.6 mM. The amount of glycine in the formulation should not cause a significant buffering effect so that antibody precipitation at
10 its isoelectric point can be avoided. Glycine may be also used in a form of a pharmaceutically acceptable salt, such as hydrochloride, hydrobromide, sulfate, acetate, etc. The purity of glycine should be at least 98%, preferably at least 99%, and most preferably 99.5%. In a specific embodiment, glycine is not included in the liquid formulations of the present invention.

15 Optionally, the formulations of the present invention may further comprise other excipients, such as saccharides (e.g., sucrose, mannose, trehalose, etc.) and polyols (e.g., mannitol, sorbitol, etc.). In one embodiment, the other excipient is a saccharide. In a specific embodiment, the saccharide is sucrose, which is at a concentration range between about 1% and about 20%, preferably about 5% and about 15%, more preferably about 3%
20 and 10%. In another embodiment, the other excipient is a polyol. Preferably, however, the liquid formulations of the present invention do not contain mannitol. In a specific embodiment, the polyol is polysorbate (e.g., Tween 20), which is at a concentration range between about 0.001% and about 1%, preferably, about 0.01 to about 0.1.

The liquid formulations of the present invention exhibit stability at the temperature
25 ranges of 38°C-42°C for at least 60 days and, in some embodiments, not more than 20 days, of 20°C-24°C for at least 1 year, of 2°C-8°C (in particular, at 4°C) for at least 3 years, at least 4 years, or at least 5 years and at -20°C for at least 3 years, at least 4 years, or at least 5 years, as assessed by high performance size exclusion chromatography (HPSEC). Namely, the liquid formulations of the present invention have low to undetectable levels of
30 aggregation and/or fragmentation, as defined herein, after the storage for the defined periods as set forth above. Preferably, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, and most preferably no more than 0.5%, of SYNAGIS® or an antigen-binding fragment thereof forms an aggregate as measured by HPSEC, after the storage for the defined periods as set forth above. Furthermore, liquid formulations of the

present invention exhibit almost no loss in biological activity(ies) of SYNAGIS[®] or an antigen-binding fragment thereof during the prolonged storage under the condition described above, as assessed by various immunological assays including, for example, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay to measure the RSV antigen-binding ability of SYNAGIS[®] or an antigen-binding fragment thereof, or, for example, by a C3a/C4a assay to measure the complement activating ability of SYNAGIS[®] or an antigen-binding fragment thereof. The liquid formulations of the present invention retain after the storage for the above-defined periods more than 80%, more than 85%, more than 90%, more than 95%, more than 98%, more than 99%, or more than 99.5% of the initial biological activity(ies) prior to the storage.

The liquid formulations of the present invention can be prepared as unit dosage forms. For example, a unit dosage per vial may contain 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of different concentrations of SYNAGIS[®] or an antigen-binding fragment thereof ranging from about 15 mg/ml to about 300 mg/ml concentration of SYNAGIS[®] or an antigen-binding fragment thereof which immunospecifically binds to a RSV. If necessary, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial.

5.1.1 SYNAGIS[®]

The invention relates to liquid formulations comprising SYNAGIS[®] or an antigen-binding fragment thereof. In a preferred embodiments, the invention provides liquid formulations of SYNAGIS[®], a humanized monoclonal antibody which neutralizes a broad range of RSV isolates. The amino acid sequence of SYNAGIS[®] is disclosed, e.g., in Johnson *et al.*, 1997, *J. Infectious Disease* 176:1215-1224, and U.S. Patent No. 5,824,307, and its V_HCDRs and V_LCDRs are shown in Table 1, *infra*. The properties and uses of SYNAGIS[®] are also disclosed in, e.g., other applications, see, e.g., U.S. Patent Application No. 09/724,396 filed November 28, 2000; U.S. Patent Application No. 09/996,265 filed November 28, 2001 and U.S. Patent Application No. 10/403,180 filed March 31, 2003, all of which are incorporated herein by reference.

Table 1. CDR Sequences of SYNAGIS[®]

CDR	Sequence	SEQ ID NO:
VH1	TSGMSVG	1
VH2	DIWWD ~~DK~~ DYNPSLKS	2

WO 03/105894		PCT/US03/18913
VH3	<u>SMTINWYFDV</u>	3
VL1	<u>KCOLSVGYMH</u>	4
VL2	<u>DTSKLAS</u>	5
VL3	<u>FQGSGYPET</u>	6

In addition, the present invention also encompasses stable liquid formulations of modified forms of SYNAGIS® or an antigen-binding fragment thereof that have improved half-lives. In particular, the present invention encompasses a modified form of SYNAGIS® or an antigen-binding fragment thereof which has a half-life in a subject, preferably a human, of greater than 3 days, greater than 7 days, greater than 10 days, preferably greater than 15 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. By prolonging the half-lives of SYNAGIS® and antigen-binding fragments thereof, it is possible to reduce the amount and/or frequency of dosing of the antibody or antigen-binding fragment.

To prolong the serum circulation of an antibody *in vivo*, various techniques can be used. For example, inert polymer molecules, such as high molecular weight polyethyleneglycol (PEG), can be attached to an antibody with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibody or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity can be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity as well as for *in vivo* efficacy using methods known to those of skilled in the art, for example, by immuncassays described herein.

An antibody having an increased half-life *in vivo* can also be generated by introducing one or more amino acid modifications (*i.e.*, substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (preferably a Fc or hinge Fc domain fragment). See, *e.g.*, International Publication No. WO 93/23289; International Publication No. WO 97/34631; and U.S. Patent No. 6,277,775, each of which is incorporated herein by reference in its entirety. SYNAGIS® and antigen-binding fragments thereof with improved *in vivo* half-lives and methods for preparing them are

WO 03/105894

PCT/US03/18913

disclosed in International Application WO 02/060919, filed December 12, 2001, and U.S. Patent Application No. 10/020,354, filed December 12, 2001, both entitled "Molecules with Extended Half-Lives, Compositions and Uses" and by L. Johnson *et al.* which are hereby incorporated by reference in their entireties.

5 Further, an antibody can be conjugated to albumin in order to make the antibody or an antigen-binding fragment thereof more stable *in vivo* or have a longer half life *in vivo*. The techniques are well known in the art, see *e.g.*, International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413, 622, all of which are incorporated herein by reference.

10 The invention further comprises liquid formulations of SYNAGIS® or antigen-binding fragments thereof that have been modified, for example, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc., and retain RSV antigen-binding activity.

15 5.1.2 Antibody Conjugates

The present invention encompasses the use of liquid formulations of SYNAGIS® or an antigen-binding fragment thereof (including modified forms that have increased *in vivo* half-lives) that conjugated to one or more moieties, including but not limited to, peptides, polypeptides, proteins, fusion proteins, nucleic acid molecules, small molecules, mimetic agents, synthetic drugs, inorganic molecules, and organic molecules.

20 The present invention encompasses the use of liquid formulations of SYNAGIS® recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or antigen-binding fragment, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, an antibody may be used to target a heterologous polypeptide to a particular cell type, either *in vitro* or *in vivo*, by fusing or conjugating the antibody to another antibody specific for particular cell surface receptors. An antibody fused or
25 conjugated to a heterologous polypeptide may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See *e.g.*, International publication No. WO 93/21232; European Patent No. EP 439,095; Naramura *et al.*, 1994, Immunol. Lett. 39:91-99; U.S. Patent No. 5,474,981; Gillies *et al.*, 1992, PNAS 89:1423-1432; and

Pell *et al.*, 1991, J. Immunol. 146:2446-2452, which are incorporated by reference in their entireties.

The present invention further includes compositions comprising a heterologous protein, peptide or polypeptide fused or conjugated to an antigen-binding fragment of SYNAGIS[®]. For example, a heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, or F(ab)₂ fragment. Methods for fusing or conjugating a polypeptide to antibody portion are known in the art. See, e.g., U.S. Patent Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi *et al.*, 1991, Proc. Natl. Acad. Sci. USA 88: 10535-10539; Zheng *et al.*, 1995, J. Immunol. 154:5590-5600; and Vil *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:11337-11341 (all references are incorporated herein by reference in their entireties)

Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of SYNAGIS[®] or fragments thereof (e.g., an antibody or an antigen-binding fragment thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.*, 1997, Curr. Opin. Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson *et al.*, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). SYNAGIS[®] or an antigen-binding fragment thereof, or the nucleic acid encoding SYNAGIS[®] or an antigen-binding fragment thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. SYNAGIS[®] or an antigen-binding fragment thereof may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, SYNAGIS[®] or an antigen-binding fragment thereof can be fused to a marker sequence, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to,

WO 03/105894

PCT/US03/18913

the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, 1984, Cell 37:767) and the "flag" tag.

The present invention also encompasses the liquid formulations of SYNAGIS® or an antigen-binding fragment thereof conjugated to a diagnostic or detectable agent or any other molecule for which serum half-life is desired to be increased. Such an antibody can be useful for monitoring or prognosing the development or progression of a RSV infection as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling SYNAGIS® or an antigen-binding fragment thereof to a detectable substance including, but not limited to, various enzymes, such as but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as but not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as but not limited to iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{115}In , ^{113}In , ^{112}In , ^{111}In), and technetium (^{99}Tc), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , and ^{117}Te ; positron emitting metals using various positron emission tomographies, nonradioactive paramagnetic metal ions, and molecules that are radiolabelled or conjugated to specific radioisotopes. The detectable substance may be coupled or conjugated either directly to SYNAGIS® or an antigen-binding fragment thereof or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, e.g., U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as a diagnostics according to the present invention.

The present invention further encompasses uses of SYNAGIS® or an antigen-binding fragment thereof conjugated to a therapeutic moiety. An antibody or antigen-binding fragment may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin,

WO 03/105894

PCT/US03/18913

daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and peromycin and analogs or homologs thereof. Therapeutic moieties include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU)), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP cisplatin); anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin); antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)); Auristatin molecules (e.g., auristatin PHE, bryostatin 1, solastatin 10, see Woyke *et al.*, Antimicrob. Agents Chemother. 46:3802-8 (2002), Woyke *et al.*, Antimicrob. Agents Chemother. 45:3580-4 (2001), Mohammad *et al.*, Anticancer Drugs 12:735-40 (2001), Wall *et al.*, Biochem. Biophys. Res. Commun. 266:76-80 (1999), Mohammad *et al.*, Int. J. Oncol. 15:367-72 (1999), all of which are incorporated herein by reference); anti-mitotic agents (e.g., vincristine and vinblastine); hormones (e.g., glucocorticoids, progestatins, androgens, and estrogens); DNA repair enzyme inhibitors (e.g., etoposide or topotecan); kinase inhibitors (e.g., compound ST1571, imatinib mesylate (Kantarjian *et al.*, Clin Cancer Res. 8(7):2167-76 (2002)), and those compounds disclosed in U.S. Pat. Nos. 6,245,759, 6,399,633, 6,383,790, 6,335,156, 6,271,242, 6,242,196, 6,218,410, 6,218,372, 6,057,300, 6,034,053, 5,985,877, 5,958,769, 5,925,376, 5,922,844, 5,911,995, 5,872,223, 5,863,904, 5,840,745, 5,728,868, 5,648,239, and 5,587,459); farnesyl transferase inhibitors (e.g., R115777, BMS 214662, and those disclosed by, for example, U.S. Patent Nos. 6,458,935, 6,451,812, 6,440,974, 6,436,960, 6,432,959, 6,420,387, 6,414,145, 6,410,541, 6,410,539, 6,403,581, 6,399,615, 6,387,905, 6,372,747, 6,369,034, 6,352,188, 6,342,765, 6,342,487, 6,300,501, 6,268,363, 6,265,422, 6,248,756, 6,239,140, 6,232,338, 6,228,865, 6,228,856, 6,225,322, 6,218,406, 6,211,193, 6,187,786, 6,159,096, 6,159,984, 6,143,766, 6,133,303, 6,127,366, 6,124,465, 6,124,295, 6,103,723, 6,093,737, 6,090,948, 6,080,870, 6,077,853, 6,071,935, 6,066,738, 6,063,930, 6,054,466, 6,051,582, 6,051,574, and 6,040,305); topoisomerase inhibitors (e.g., camptothecin, irinotecan, SN 38, topotecan, 9 aminocamptothecin, GG 211 (GI 147211), DX 8951f, IST 622, rubitecan, pyrazoloacridine, XR 5000, saintopin, UCE6, UCE1022, TAN 1518A, TAN 1518B, KT6006, KT6528, ED 110, NB 506, ED 110, NB 506, rebeccamycin, and bulgarein); DNA minor groove binders such as Hoechst dye 33342 and Hoechst dye 33258; nitidine; fagaronine; epiberberine; coralyn; beta lapachone; BC 4 1; and pharmaceutically

acceptable salts, solvates, clathrates, and prodrugs thereof (See, *e.g.*, Rothenberg, M.L., *Annals of Oncology* 8:837-855(1997); and Moreau *et al.*, *J. Med. Chem.* 41:1631-1640(1998)). Therapeutic moieties may also be antisense oligonucleotides (*e.g.*, those disclosed in the U.S. Pat. Nos. 6,277,832, 5,998,596, 5,885,834, 5,734,033, and 5,618,709); immunomodulators (*e.g.*, antibodies and cytokines); antibodies (*e.g.*, rituximab (Rituxan®), calicheamycin (Mylotarg®), ibritumomab tiuxetan (Zevalin®), and tositumomab (Bexxar®)); and adenosine deaminase inhibitors (*e.g.*, Fludarabine phosphate and 2-Deoxy-2-fluorodeoxyadenosine).

Further, an antibody or an antigen-binding fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moiety or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.*, TNF- α , TNF- β , AIM I (see, International publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, 1994, *J. Immunol.*, 6:1567-1574), and VEGF (see, International publication No. WO 99/23105); or, a biological response modifier such as, for example, a lymphokine (*e.g.*, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-4 ("IL-4"), interleukin-6 ("IL-6"), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-12 (IL-12), interferon- α , β , γ , granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (*e.g.*, growth hormone ("GH")).

Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive metal ion, *e.g.*, alpha-emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In , ^{131}Lu , ^{131}Y , ^{131}Ho , ^{151}Sm , to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, 1998, *Clin Cancer Res.* 4(10):2483-90; Petersen *et al.*, 1999, *Bioconjug. Chem.* 10(4):553-7; and Zimmerman *et al.*, 1999, *Nucl. Med. Biol.* 25(8):943-50, each incorporated by reference in their entireties.

645 415

Techniques for conjugating therapeutic moieties to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-55 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies 84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, 1982, *Immunol. Rev.* 62:119-58.

Alternatively, SYNAGIS® or an antigen-binding fragment thereof can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

SYNAGIS® or an antigen-binding fragment thereof may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

The therapeutic moiety or drug conjugated to SYNAGIS® or an antigen-binding fragment thereof should be chosen to achieve the desired prophylactic or therapeutic effect(s) for a RSV infection in a subject. A clinician or other medical professional should consider the following when deciding on which therapeutic moiety or drug to conjugate to SYNAGIS® or an antigen-binding fragment thereof: the severity of the infection, and the condition of the subject.

SYNAGIS® or an antigen-binding fragment thereof, with or without a therapeutic moiety conjugated to it, can be used as a therapeutic.

5.2 Method of Preparing the Antibody Formulations

The present invention provides methods for preparing liquid formulations of SYNAGIS® or an antigen-binding fragment thereof. Figure 1 is a schematic diagram showing the outline for preparing purified SYNAGIS®. The methods for preparing liquid formulations of the present invention comprise: purifying the antibody from conditioned medium (either single lots or pooled lots of medium) and concentrating a fraction containing the purified SYNAGIS® to a final antibody concentration of from about 1.5

mg/ml, about 20 mg/ml, about 30 mg/ml, about 40 mg/ml, about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 150 mg/ml, about 200 mg/ml, about 250 mg/ml, or about 300 mg/ml using a semipermeable membrane with an appropriate molecular weight (MW) cutoff (e.g., 30 kD cutoff for whole antibody molecules and F(ab')₂ fragments; and 10 kD cutoff for antibody fragments, such as Fab fragments) and diafiltrating the concentrated antibody fraction into the formulation buffer using the same membrane. The formulation buffer of the present invention comprises histidine at a concentration from about 1 mM to about 100 mM, about 10 mM to about 50 mM, about 20 mM to about 30 mM, or about 23 mM to about 27 mM, and is most preferably about 25 mM. The formulations may further comprise glycine at a concentration of less than 100 mM, less than 50 mM, less than 3.0 mM, less than 2.0 mM, or less than 1.6 mM, and most preferably of 1.6 mM. The amount of glycine in the formulation should not cause a significant buffering in order to avoid antibody precipitation at its isoelectric point. The pH of the formulation may range from about 5.0 to about 7.0, preferably about 5.5 to about 6.5, more preferably about 5.8 to about 6.2, and most preferably about 6.0. To obtain an appropriate pH for a particular antibody, it is preferable that histidine (and glycine, if added) is first dissolved in water to obtain a buffer solution with higher pH than the desired pH and then the pH is brought down to the desired level by adding HCl. This way, the formation of inorganic salts (e.g., formation of NaCl when, for example, histidine hydrochloride is used as histidine and pH is raised to a desired level by adding NaOH) can be avoided.

The liquid formulations of the present invention can be prepared as unit dosage forms by preparing a vial containing an aliquot of the liquid formulation for a one-time use. For example, a unit dosage per vial may contain 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of different concentrations of SYNAGIS® or an antigen-binding fragment thereof ranging from about 15 mg/ml to about 300 mg/ml concentration of SYNAGIS® or an antigen-binding fragment thereof which immunospecifically binds to a RSV. If necessary, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial.

The liquid formulations of the present invention may be sterilized by various sterilization methods, including sterile filtration, radiation, etc. In a most preferred embodiment, the diafiltrated antibody formulation is filter-sterilized with a presterilized 0.2 or 0.22-micron filter. Sterilized liquid formulations of the present invention may be

administered to a subject to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof.

Although the invention is directed to liquid non-lyophilized formulations, it should be noted for the purpose of equivalents that the formulations of the invention may be lyophilized if desired. Thus, the invention encompasses lyophilized forms of the formulations of the invention although such lyophilized formulations are not necessary and thus not preferred.

5.5 Methods of Preparing SYNAGIS®

SYNAGIS® and an antigen-binding fragment thereof contained in the liquid formulations of the present invention can be prepared by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or, preferably, by recombinant expression techniques.

The nucleotide sequence encoding the heavy and light chain variable domains of SYNAGIS® may be obtained from, for example, co-pending application 09/724,396, filed November 28, 2000 and 09/996,265, filed November 28, 2001, both by Young *et al.*, and both of which are incorporated by reference herein in its entirety. See also, U.S. Patent No. 5,824,307 by Johnson *et al.* In certain embodiments, a nucleic acid encoding SYNAGIS® or an antigen-binding fragment thereof may be chemically synthesized or assembled from oligonucleotides as well known in the art, and then amplified by PCR, cloning or other method known in the art.

Recombinant expression of an antibody (such as SYNAGIS®) requires construction of an expression vector containing a nucleotide sequence that encodes the antibody. Once a nucleotide sequence encoding an antibody molecule or a heavy or light chain of an antibody, or an antigen-binding fragment thereof has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art as discussed in the previous sections. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The nucleotide sequence encoding the heavy-chain variable region, light-chain variable region, both the heavy-chain and light-chain variable regions, an epitope-binding fragment of the heavy- and/or light-chain variable region, or one or more complementarity determining regions (CDRs) of an

antibody may be cloned into such a vector for expression. Thus-prepared expression vector can be then introduced into appropriate host cells for the expression of the antibody. Accordingly, the invention includes host cells containing a polynucleotide encoding S/NAGIS[®] or an antigen-binding fragment thereof.

5 The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides or different selectable markers to ensure maintenance of both plasmids. Alternatively, a single vector may be used
10 which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature*, 322:52, 1986; and Kohler, *Proc. Natl. Acad. Sci. USA*, 77:2 197, 1980). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

15 For long-term, high-yield production of recombinant antibodies, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation
20 sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell
25 lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

 A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, *Cell*, 11:223, 1977), hypoxanthineguanine
30 phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA*, 48:202, 1992), and adenine phosphoribosyltransferase (Lowy *et al.*, *Cell*, 22:8-17, 1980) genes can be employed in tk⁻, hgp⁺ or apr⁺ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, *Natl. Acad. Sci. USA*, 77:357, 1980 and O'Hare *et al.*, *Proc.*

WO 03/105894

PCT/US03/18913

Natl. Acad. Sci. USA, 78:1527, 1981); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA*, 78:2072, 1981); *neo*, which confers resistance to the aminoglycoside G-418 (Wu and Wu, *Biotherapy*, 3:87-95, 1991; Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.*, 32:573-596, 1993; Mulligan, *Science*, 260:926-932, 1993; and Morgan and Anderson, *Ann. Rev. Biochem.*, 62: 191-217, 1993; and May, *TTB TECH*, 11(5):155-215, 1993); and *hygro*, which confers resistance to hygromycin (Senterre *et al.*, *Gene*, 30:147, 1984). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel *et al.* (eds.), 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; Kriegler, 1990, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY; in Chapters 12 and 13. Dracopoli *et al.* (eds.), 1994, *Current Protocols in Human Genetics*, John Wiley & Sons, NY; and Colberre-Garapin *et al.*, *J. Mol. Biol.*, 150:1, 1981, which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, 1987, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. Academic Press, New York). When a marker in the vector system expressing antibody is amplifiable, increasing in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse *et al.*, *Mol., Cell. Biol.*, 3:257, 1983).

Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A purification, and sizing column chromatography), centrifugation, differential solubility, or by any other standard techniques for the purification of proteins. Further, SYNAGIS® or an antigen-binding fragment thereof may be fused to heterologous protein, polypeptide or peptide sequences described herein or otherwise known in the art to facilitate purification.

Antigen-binding fragments of SYNAGIS® that immunospecifically bind RSV may be generated by known techniques. For example, Fab and F(ab')₂ fragments may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂

69051

fragments contain the complete light chain, and the variable region, the CH1 region and the hinge region of the heavy chain.

5.4 Methods of Monitoring the Stability And Aggregation of Antibody Formulations

5 There are various methods available for assessing the stability of protein formulations, including antibody formulations, based on the physical and chemical structures of the proteins as well as on their biological activities. For example, to study denaturation of proteins, methods such as charge-transfer absorption, thermal analysis, fluorescence spectroscopy, circular dichroism, NMR, and HPSEC, are available. See, for example, Wang *et al.*, 1988, J. of Parenteral Science & Technology 42(supp):S4-S26. The rCGE, and HPSEC are the most common and simplest methods to assess the formation of protein aggregates, protein degradation and protein fragmentation. Accordingly, the stability of the liquid formulations of the present invention may be assessed by these methods.

15 For example, the stability of the liquid formulations of the present invention may be evaluated by HPSEC or rCGE, wherein the percentage area of the peaks represents the non-degraded SYNAGIS[®] or non-degraded antigen-binding fragments of SYNAGIS[®]. In particular, approximately 250 µg of SYNAGIS[®] or an antigen-binding fragment thereof (approximately 25 µl of a liquid formulation comprising 10 mg/ml of SYNAGIS[®] or an antigen-binding fragment thereof) is injected onto a TOSOH TSK G3000SW_{XL} column (7.8 mm x 30 cm) fitted with a TSK SW x1 guard column (6.0 mm x 4.0 cm), SYNAGIS[®] or an antigen-binding fragment thereof is eluted isocratically with 0.1 M disodium phosphate containing 0.1 M sodium sulfate and 0.05% sodium azide, at a flow rate of 0.8 to 1.0 ml/min. Eluted protein is detected using UV absorbance at 280 nm. SYNAGIS[®] reference standard is run in the assay as a control, and the results are reported as the area percent of the product monomer peak compared to all other peaks excluding the included volume peak observed approximately at 12 to 14 minutes. Peaks eluting earlier than the monomer peak are recorded as percent aggregate.

25 The liquid formulations of the present invention exhibit low to undetectable levels of aggregation as measured by HPSEC or rCGE, that is, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1%, and most preferably no more than 0.5% aggregate by weight protein, and low to undetectable levels of fragmentation, that is, 80% or higher, 85% or higher, 90% or higher, 95% or higher, 98% or higher, or 99% or higher, or 99.5% or higher of the total peak area in the peak(s) representing intact antibodies

or fragments thereof. In the case of SDS-PAGE, the density or the radioactivity of each band stained or labeled with radioisotope can be measured and the % density or % radioactivity of the band representing non-degraded SYNAGIS[®] or antigen-binding fragments thereof can be obtained.

5 The stability of the liquid formulations of the present invention can be also assessed by any assays which measures the biological activity SYNAGIS[®] or an antigen-binding fragment thereof in the formulation. The biological activities of an antibody include, but not limited to, antigen-binding activity, complement-activation activity, Fc-receptor binding activity, and so forth. Antigen-binding activity of SYNAGIS[®] or an antigen-binding
10 fragment thereof can be measured by any method known to those skilled in the art, including but not limited to ELISA, radioimmunoassay, Western blot, and the like. Complement-activation activity can be measured by a C3a/C4a assay in the system where SYNAGIS[®] or an antigen-binding fragment thereof is reacted in the presence of the complement components with cells expressing a RSV antigen. *Also see Harlow et al.,*
15 *Antibodies. A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety). An ELISA based assay, *e.g.*, may be used to compare the ability of a liquid formulation of SYNAGIS[®] or an antigen-binding fragment thereof to immunospecifically bind to a RSV antigen to a SYNAGIS[®] reference standard. In this assay, plates are coated with RSV antigen (in particular, the A antigenic site of F
20 protein of RSV) and the binding signal of a set concentration of a SYNAGIS[®] reference standard is compared to the binding signal of the same concentration of the liquid formulation of SYNAGIS[®] or an antigen-binding fragment thereof.

 The purity of the liquid antibody formulations of the invention may be measured by any method well-known to one of skilled in the art such as, *e.g.*, HPSEC. The sterility of
25 the liquid antibody formulations may be assessed as follows: sterile soybean-casein digest medium and fluid thioglycollate medium are inoculated with a test liquid antibody formulation by filtering the liquid antibody formulation through a sterile filter having a nominal porosity of 0.45 μ m. When using the Sterisure[™] or Steritest[™] method, each filter device is aseptically filled with approximately 100 ml of sterile soybean-casein digest
30 medium or fluid thioglycollate medium. When using the conventional method, the challenged filter is aseptically transferred to 100 ml of sterile soybean-casein digest medium or fluid thioglycollate medium. The media are incubated at appropriate temperatures and observed three times over a 14 day period for evidence of bacterial or fungal growth.

5.5 Prophylactic And Therapeutic Utility Of The Antibody Formulations

The present invention is also directed to antibody-based therapies which involve administering to a subject, preferably a mammal, most preferably a human, the liquid antibody formulations of the present invention for preventing, treating, managing or
5 ameliorating a RSV infection or one or more symptoms thereof. Prophylactic and therapeutic formulations of the invention comprise SYNAGIS® or an antigen-binding fragment thereof at concentrations of from about 15 mg/ml to about 300 mg/ml in a solution containing histidine.

The liquid formulations of the invention may comprise modified SYNAGIS® or
10 antigen-binding fragments thereof that have improved *in vivo* half-lives compared to known antibodies that immunospecifically binds to a RSV antigen (e.g., unmodified SYNAGIS®).

In one embodiment, the liquid formulations of the present invention are administered to a mammal, preferably a human, to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. In another embodiment, the liquid
15 formulations of the invention are administered to a human with cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency, or to a human who has had a bone marrow transplant to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. In another embodiment, the liquid formulations of the invention are administered to a human
20 infant, preferably a human infant born prematurely or a human infant at risk of hospitalization for a RSV infection to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. In another embodiment, the liquid formulations of the invention are administered to an elderly person to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. In yet another embodiment, the liquid
25 formulations of the invention are administered to a subject in an institution or group home (e.g., a nursing home or orphanage).

The liquid formulations of the present invention may be used locally or systemically in the body of a subject prophylactically or therapeutically. The formulations of the present invention may also be advantageously utilized in combination with other therapies useful in
30 the prevention, treatment, management or amelioration of a RSV infection (e.g., a prophylactic or a therapeutic agent other than SYNAGIS®). Non-limiting examples of prophylactic or therapeutic agents that can be used in combination with the liquid formulations of the present invention, see Section 5.6, *infra*.

When one or more other therapies are used, they can be administered separately, in any appropriate form and by any suitable route. A liquid formulation of the invention may be administered to a mammal, preferably a human, concurrently with one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof. The term "concurrently" is not limited to the administration of therapies at exactly the same time, but rather it is meant that a liquid formulation of the invention and another therapy are administered to a mammal in a sequence and within a time interval such that SYNAGIS® or an antigen-binding fragment thereof contained in the liquid formulation can act together with the other therapy to provide an increased benefit than if they were administered otherwise. For example, a liquid formulation of the invention and one or more other prophylactic or therapeutic agents useful for prevention, treatment, management or amelioration of a RSV infection may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect.

In various embodiments, a liquid formulation of the invention and one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for prevention, treatment, management or amelioration of a RSV infection or a symptom thereof are administered less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In preferred embodiments, a liquid formulation of the invention and one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for prevention, treatment, management or amelioration of a RSV infection or a symptom thereof are administered within the same patient visit. In other embodiments, a liquid formulation of the invention and one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for prevention, treatment, management or amelioration of a RSV infection or a symptom thereof are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week apart, at about 1 to 2 weeks apart, or more than 2 weeks apart. In preferred embodiments, a liquid formulation of the invention and

one or more other prophylactic or therapeutic agents useful for prevention, treatment, management or amelioration of a RSV infection or a symptom thereof are administered in a time frame where both agents are still active. One skilled in the art would be able to determine such a time frame by determining the half-life of the administered agents.

5 In certain embodiments, a liquid formulation of the invention and one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for prevention, treatment, management or amelioration of a RSV infection or a symptom thereof are cyclically administered to a subject. Cycling therapy involves the administration of a first therapy for a period of time, followed by the administration of a second therapy and/or third
10 therapy for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In certain embodiments, a liquid formulation of the invention and one or more other therapies (e.g., one or more other prophylactic or therapeutic agents) useful for prevention,
15 treatment, management or amelioration of a RSV infection or a symptom thereof are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a therapy (e.g., a therapeutic or prophylactic agent) by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at
20 least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a
25 preferred embodiment, human or humanized antibodies, fragments derivatives, or analogs, are administered to a human patient for therapy or prophylaxis.

5.6 Agents Useful in Combination with SYNAGIS® Formulations

The present invention provides methods for preventing, managing, treating, or ameliorating a RSV infection or one or more symptoms thereof comprising administering to
30 a subject in need thereof a liquid formulation of the invention alone or in combination with one or more therapies (e.g., one or more prophylactic or therapeutic agents) other than SYNAGIS®. The present invention provides methods for preventing, treating, managing or ameliorating a RSV infection or one or more symptoms thereof comprising administering to

695 sb

a subject in need thereof a liquid formulation of the invention alone or in combination with one or more therapies (e.g., one or more prophylactic or therapeutic agents) other than SYNAGIS®. The present invention also provides compositions comprising a liquid formulation of SYNAGIS® or an antigen-binding fragment thereof and one or more prophylactic or therapeutic agents other than SYNAGIS® and methods of preventing, treating, managing or ameliorating a RSV infection or one or more symptoms thereof utilizing said compositions. Therapeutic or prophylactic agents include, but are not limited to, small molecules, synthetic drugs, peptides, polypeptides, proteins, nucleic acids (e.g., DNA and RNA nucleotides including, but not limited to, antisense nucleotide sequences, triple helices, RNA interference (RNAi), and nucleotide sequences encoding biologically active proteins, polypeptides or peptides) antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules.

Any therapy which is known to be useful, or which has been used or is currently being used for the prevention, management, treatment, or amelioration of a RSV infection or one or more symptoms thereof can be used in combination with a liquid formulation in accordance with the invention described herein. See, e.g., Gilman *et al.*, *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 10th ed., McGraw-Hill, New York, 2001; *The Merck Manual of Diagnosis and Therapy*, Berkow, M.D. *et al.* (eds.), 17th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, 1999; *Cecil Textbook of Medicine*, 20th Ed., Bennett and Plum (eds.), W.B. Saunders, Philadelphia, 1996, for information regarding therapies (e.g., prophylactic or therapeutic agents) which have been or are currently being used for preventing, treating, managing, or ameliorating a RSV infection or one or more symptoms thereof. Examples of such agents include, but are not limited to, immunomodulatory agents, anti-inflammatory agents (e.g., adrenocorticoids, corticosteroids (e.g., beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, methylprednisolone, prednisolone, prednisone, hydrocortisone), glucocorticoids, steroids, non-steroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen, diclofenac, and COX-2 inhibitors), pain relievers, leukotriene antagonists (e.g., montelukast, methyl xanthines, zafirlukast, and zileuton), beta2-agonists (e.g., albuterol, biterol, fenoterol, isoecharine, metaproterenol, pirbuterol, salbutamol, terbutalin formoterol, salmeterol, and salbutamol terbutaline), anticholinergic agents (e.g., ipratropium bromide and oxitropium bromide), sulphasalazine, penicillamine, dapsone, antihistamines, anti-malarial agents (e.g., hydroxychloroquine)), and anti-viral agents.

656 57

In specific embodiments, a liquid formulation of the invention is used in combination with a monoclonal or chimeric antibody, or with a lymphokine or hematopoietic growth factor (such as, *e.g.*, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, and interferon α , β , and γ), which, for example, serves to increase the number or activity of effector cells which interact with the antibody. A liquid formulation of the present invention may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, and interferon α , β , and γ), which, for example, serve to increase the immune response. The liquid formulations of the present invention may also be advantageously utilized in combination with one or more drugs used to treat RSV infection such as, for example anti-viral agents. The liquid formulations of the present invention may be used in combination with one or more of the following drugs: NIH-351 (Gemini Technologies), recombinant RSV vaccine (MedImmune Vaccines, Inc. U.S. Application Nos. 60/358,934 filed February 21, 2002, 10/373,567 filed February 21, 2003, 10/371,099 filed February 21, 2003, 10/371,122 filed February 21, 2003, 10/371,264 filed February 21, 2003, 60/466,181 filed April 25, 2003 and 60/465,811 filed April 25, 2003, all of which are incorporated herein by reference), RSVf-2 (Intracel), F-50042 (Pierre Fabre), T-786 (Trimeris), VP-36676 (ViroPharma), RFI-641 (American Home Products), VP-14637 (ViroPharma), PFP-1 and PFP-2 (American Home Products), RSV vaccine (Avant Immunotherapeutics), and F-50077 (Pierre Fabre).

5.6.1 Immunomodulatory Agents

Any immunomodulatory agent well-known to one of skilled in the art may be used in accordance with the methods of the invention to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. Immunomodulatory agents can affect one or more or all aspects of the immune response in a subject. Aspects of the immune response include, but are not limited to, the inflammatory response, the complement cascade, leukocyte and lymphocyte differentiation, proliferation, and/or effector function, monocyte and/or basophil counts, and the cellular communication among cells of the immune system. In certain embodiments of the invention, an immunomodulatory agent modulates one aspect of the immune response. In other embodiments, an immunomodulatory agent modulates more than one aspect of the immune response. In a preferred embodiment of the invention, the administration of an immunomodulatory agent to a subject inhibits or reduces one or more aspects of the subject's immune response capabilities. In an alternative embodiment

of the invention, the immunomodulatory agent enhances one or more aspects of a subject's immune response. In certain embodiments, an immunomodulatory agent is not an anti-inflammatory agent. In a specific embodiment, an immunomodulatory agent is an agent other than a chemotherapeutic agent.

5 Examples of immunomodulatory agents include, but are not limited to, proteinaceous agents such as cytokines, peptide mimetics, and antibodies (*e.g.*, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or F(ab)₂ fragments or epitope binding fragments), nucleic acid molecules (*e.g.*, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. In particular, immunomodulatory agents include, but are not limited to, methotrexate, 10 leflunomide, cyclophosphamide, cytoxan, Immuran, cyclosporine A, minocycline, azathioprine, antibiotics (*e.g.*, FK506 (tacrolimus)), methylprednisolone (MP), corticosteroids, steroids, mycophenolate mofetil, rapamycin (sirolimus), mizoribine, deoxyspergualin, brequinar, malononitriloamides (*e.g.*, leflunamide), T cell receptor 15 modulators, and cytokine receptor modulators.

 Examples of T cell receptor modulators include, but are not limited to, anti-T cell receptor antibodies (*e.g.*, anti-CD4 antibodies (*e.g.*, cM-T412 (Boeringer), IDEC-CE9.1@ (IDEC and SKB), mAB 4162W94, Orthoclone and OKTcd4a (Janssen-Cilag)), anti-CD3 antibodies (*e.g.*, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), or Rituxan 20 (IDEC)), anti-CD5 antibodies (*e.g.*, an anti-CD5 ricin-linked immunoconjugate), anti-CD7 antibodies (*e.g.*, CHH-380 (Novartis)), anti-CD8 antibodies, anti-CD40 ligand monoclonal antibodies (*e.g.*, IDEC-131 (IDEC)), anti-CD52 antibodies (*e.g.*, CAMPATH 1H (Ilex)), anti-CD2 antibodies (*e.g.*, MEDI-507 (MedImmune, Inc., International Publication Nos. W/C 02/098370 and WO 02/069904)), anti-CD11a antibodies (*e.g.*, Xancima (Genentech)), 25 and anti-B7 antibodies (*e.g.*, IDEC-114 (IDEC))), CTLA4-immunoglobulin, and LFA-3TIP (Biogen, International Publication No. WO 93/08656 and U.S. Patent No. 6,162,432).

 Examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (*e.g.*, the extracellular domain of a TNF- α receptor or an antigen-binding 30 fragment thereof, the extracellular domain of an IL-1 β receptor or an antigen-binding fragment thereof, and the extracellular domain of an IL-6 receptor or an antigen-binding fragment thereof), cytokines or fragments thereof (*e.g.*, interleukin IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-23, TNF- α , TNF- β , interferon (IFN)- α , IFN- β , IFN- γ , and GM-CSF), anti-cytokine receptor antibodies (*e.g.*, anti-IFN receptor antibodies, anti-IL-2 receptor antibodies (*e.g.*, Zenapax (Protein Design Labs)),

anti-IL-3 receptor antibodies, anti-IL-4 receptor antibodies, anti-IL-6 receptor antibodies, anti-IL-9 receptor antibodies, anti-IL-10 receptor antibodies, anti-IL-12 receptor antibodies, anti-IL-13 receptor antibodies, anti-IL-15 receptor antibodies, and anti-IL-23 receptor antibodies), anti-cytokine antibodies (e.g., anti-IFN antibodies, anti-TNF- α antibodies, anti-IL-1 β antibodies, anti-IL-3 antibodies, anti-IL-6 antibodies, anti-IL-8 antibodies (e.g., ABX IL-8 (Abgenix)), anti-IL-9 antibodies, anti-IL-12 antibodies, anti-IL-13 antibodies, anti-IL-15 antibodies, and anti-IL-23 antibodies).

In a specific embodiment, a cytokine receptor modulator is IFN, IL-2, IL-3, IL-4, IL-10, IL-12 or an antigen-binding fragment thereof. In another embodiment, a cytokine receptor modulator is an anti-IL-1 β antibody, anti-IL-6 antibody, anti-IL-9 antibody, anti-IL-12 receptor antibody, or anti-TNF- α antibody. In another embodiment, a cytokine receptor modulator is the extracellular domain of a TNF- α receptor or an antigen-binding fragment thereof.

An immunomodulatory agent may be selected to interfere with the interactions between the T helper subsets (TH1 or TH2) and B cells to inhibit neutralizing antibody formation. Antibodies that interfere with or block the interactions necessary for the activation of B cells by TH (T helper) cells, and thus block the production of neutralizing antibodies, are useful as immunomodulatory agents in the methods of the invention. For example, B cell activation by T cells requires certain interactions to occur (Durie *et al.*, Immunol. Today, 15(9):406-410 (1994)), such as the binding of CD40 ligand on the T helper cell to the CD40 antigen on the B cell, and the binding of the CD28 and/or CTLA4 ligands on the T cell to the B7 antigen on the B cell. Without both interactions, the B cell cannot be activated to induce production of the neutralizing antibody.

The CD40 ligand (CD40L)-CD40 interaction is a desirable point to block the immune response because of its broad activity in both T helper cell activation and function as well as the absence of redundancy in its signaling pathway. Thus, in a specific embodiment of the invention, the interaction of CD40L with CD40 is transiently blocked at the time of administration of one or more of the immunomodulatory agents. This can be accomplished by treating with an agent which blocks the CD40 ligand on the T cell and interferes with the normal binding of CD40 ligand on the T helper cell with the CD40 antigen on the B cell. An antibody to CD40 ligand (anti-CD40L) (available from Bristol-Myers Squibb Co; see, e.g., European patent application 555,880, published Aug. 13, 1993) or a soluble CD40 molecule can be selected and used as an immunomodulatory agent in accordance with the methods of the invention.

An immunomodulatory agent may be selected to inhibit the interaction between TH1 cells and cytotoxic T lymphocytes ("CTLs") to reduce the occurrence of CTL-mediated killing. An immunomodulatory agent may be selected to alter (e.g., inhibit or suppress) the proliferation, differentiation, activity and/or function of the CD4⁺ and/or CD8⁺ T cells. For example, antibodies specific for T cells can be used as immunomodulatory agents to deplete, or alter the proliferation, differentiation, activity and/or function of CD4⁺ and/or CD8⁺ T cells.

In one embodiment, an immunomodulatory agent which reduces or inhibits one or more biological activities (e.g., the differentiation, proliferation, and/or effector functions) of TH0, TH1, and/or TH2 subsets of CD4⁺ T helper cells is administered to a subject with a RSV infection in accordance with the methods of the invention. One example of such an immunomodulatory agent is IL-4. IL-4 enhances antigen-specific activity of TH2 cells at the expense of the TH1 cell function (see, e.g., Yokota *et al*, 1986 Proc. Natl. Acad. Sci., USA, 83:5894-5898; and U.S. Pat. No. 5,017,691). Other examples of immunomodulatory agents that affect the biological activity (e.g., proliferation, differentiation, and/or effector functions) of T-helper cells (in particular, TH1 and/or TH2 cells) include, but are not limited to, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-23, and interferon (IFN)- γ .

In another embodiment, an immunomodulatory agent administered to a subject with a RSV infection in accordance with the methods of the invention is a cytokine that prevents antigen presentation. In a specific embodiment, an immunomodulatory agent used in the methods of the invention is IL-10. IL-10 also reduces or inhibits macrophage action which involves bacterial elimination.

In accordance with the invention, one or more immunomodulatory agents are administered to a subject with a RSV infection prior to, subsequent to, or concomitantly with a liquid formulation of SYNAGIS[®] or an antigen-binding fragment thereof. Preferably, one or more immunomodulatory agents are administered in combination with a liquid formulation of SYNAGIS[®] or an antigen-binding fragment thereof to a subject with a RSV infection to reduce or inhibit one or more aspects of the immune response as deemed necessary by one of skilled in the art. Any technique well-known to one skilled in the art can be used to measure one or more aspects of the immune response in a particular subject, and thereby determine when it is necessary to administer an immunomodulatory agent to said subject. In a preferred embodiment, a mean absolute lymphocyte count of approximately 500 cells/mm³, preferably 600 cells/mm³, 650 cells/mm³, 700 cells/mm³, 750 cells/mm³, 800 cells/mm³, 900 cells/mm³, 1000 cells/mm³, 1100 cells/mm³, or 1200

cells/mm³ is maintained in a subject. In another preferred embodiment, a subject with a RSV infection is not administered an immunomodulatory agent if their absolute lymphocyte count is 500 cells/mm³ or less, 550 cells/mm³ or less, 600 cells/mm³ or less, 650 cells/mm³ or less, 700 cells/mm³ or less, 750 cells/mm³ or less, or 800 cells/mm³ or less.

5 In a specific embodiment, one or more immunomodulatory agents are administered in combination with a liquid formulation of SYNAGIS® or an antigen-binding fragment thereof to a subject with a RSV infection so as to transiently reduce or inhibit one or more aspects of the immune response. Such a transient inhibition or reduction of one or more aspects of the immune system can last for hours, days, weeks, or months. Preferably, the
10 transient inhibition or reduction in one or more aspects of the immune response lasts for a few hours (e.g., 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 14 hours, 16 hours, 18 hours, 24 hours, 36 hours, or 48 hours), a few days (e.g., 3 days, 4 days, 5 days, 6 days, 7 days, or 14 days), or a few weeks (e.g., 3 weeks, 4 weeks, 5 weeks or 6 weeks). The transient reduction or inhibition of one or more aspects of the immune response enhances the
15 prophylactic and/or therapeutic effect(s) of a liquid formulation of SYNAGIS® or an antigen-binding fragment thereof.

In a preferred embodiment, proteins, polypeptides or peptides (including antibodies) that are utilized as immunomodulatory agents are derived from the same species as the recipient of the proteins, polypeptides or peptides so as to reduce the likelihood of an
20 immune response to those proteins, polypeptides or peptides. In another preferred embodiment, when the subject is a human, the proteins, polypeptides, or peptides that are utilized as immunomodulatory agents are human or humanized.

Nucleic acid molecules encoding proteins, polypeptides, or peptides with immunomodulatory activity or proteins, polypeptides, or peptides with immunomodulatory
25 activity can be administered to a subject with a RSV infection in accordance with the methods of the invention. Further, nucleic acid molecules encoding derivatives, analogs, or fragments of proteins, polypeptides, or peptides with immunomodulatory activity, or derivatives, analogs, or fragments of proteins, polypeptides, or peptides with immunomodulatory activity can be administered to a subject with a RSV infection in
30 accordance with the methods of the invention. Preferably, such derivatives, analogs, and fragments retain the immunomodulatory activity of the full-length, wild-type protein, polypeptide, or peptide.

Preferably, agents that are commercially available and known to function as immunomodulatory agents are used in the methods of the invention. The

immunomodulatory activity of an agent can be determined *in vitro* and/or *in vivo* by any technique well-known to one skilled in the art, including, *e.g.*, by CTL assays, proliferation assays, and immunoassays (*e.g.* ELISAs) for the expression of particular proteins such as co-stimulatory molecules and cytokines.

5.6.2 Anti-inflammatory Agents

Any anti-inflammatory agent, including agents useful in therapies for inflammatory disorders, well-known to one of skilled in the art can be used in accordance with methods of the invention to prevent, treat, manage, or ameliorate a RSV infection or one or more symptoms thereof. Non-limiting examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs, anticholinergics (*e.g.*, atropine sulfate, atropine methylnitrate, and ipratropium bromide (ATROVENTTM)), beta2-agonists (*e.g.*, albuterol (VENTOLINTM and PROVENTILTM), bitolterol (TORNALATETM), levalbuterol (XOPONEXTM), metaproterenol (ALUPENTTM), pirbuterol (MAXAIRTM), terbutaline (BRETHAIRETM and BRETHINETM), albuterol (PROVENTILTM, REPETABSTM, and VOLMAXTM), formoterol (FORADIL AEROLIZERTM), and salmeterol (SEREVENTTM and SEREVENT DISKUSTM)), and methylxanthines (*e.g.*, theophylline (UNIPHYLTM, THEO-DURTM, SLO-BIDTM, and THEO-42TM)). Examples of NSAIDs include, but are not limited to, aspirin, ibuprofen, celecoxib (CELEBREXTM), diclofenac (VOLTARENTM), etodolac (LODINETM), fenoprofen (NALFONTM), indomethacin (INDOCINTM), ketoralac (TORADOLTM), oxaprozin (DAYPROTM), nabumetone (RELAFENTM), sulindac (CLINORILTM), tolmetin (TOLECTINTM), rofecoxib (VIOXXTM), naproxen (ALEVETM, NAPROSYNTM), ketoprofen (ACTRONTM) and nabumetone (RELAFENTM). Such NSAIDs function by inhibiting a cyclooxygenase enzyme (*e.g.*, COX-1 and/or COX-2). Examples of steroidal anti-inflammatory drugs include, but are not limited to, glucocorticoids, dexamethasone (DECADRONTM), corticosteroids (*e.g.*, methylprednisolone (MEDROLTM)), cortisone, hydrocortisone, prednisone (PREDNISONTM and DELTASONTM), prednisolone (PRELONTM and PEDIAPREDTM), triamcinolone, azulfidine, and inhibitors of eicosanoids (*e.g.*, prostaglandins, thromboxanes, and leukotrienes (see Table 2, *infra*, for non-limiting examples of leukotriene and typical dosages of such agents)).

5.6.3 Anti-Viral Agents

Any anti-viral agent well-known to one of skilled in the art (in particular, one useful for the treatment, prevention, management, or amelioration of a RSV infection) can be used

in accordance with the methods of the invention to prevent, treat, manage or ameliorate a RSV infection or one or more symptoms thereof. Non-limiting examples of anti-viral agents include proteins, polypeptides, peptides, fusion proteins antibodies, nucleic acid molecules, organic molecules, inorganic molecules, and small molecules that inhibit and/or
5 reduce the attachment of a virus to its receptor, the internalization of a virus into a cell, the replication of a virus, or release of virus from a cell. In particular, anti-viral agents include, but are not limited to, nucleoside analogs (e.g., zidovudine, acyclovir, gangcyclovir, vidarabine, idoxuridine, trifluridine, and ribavirin), foscarnet, amantadine, rimantadine, saquinavir, indinavir, ritonavir, alpha-interferons and other interferons, and AZT.

10 In specific embodiments, the anti-viral agent is an antibody agent other than SYNAGIS® that is immunospecific for a viral antigen. As used herein, the term "viral antigen" includes, but is not limited to, any RSV peptide, polypeptide and protein (e.g., RSV F glycoprotein and RSV G glycoprotein) that is capable of eliciting an immune response.

15 In preferred embodiments, the viral infection is RSV and the anti-viral antigen is an antibody other than SYNAGIS® that immunospecifically binds to an antigen of RSV. In certain embodiments, the anti-RSV-antigen antibody immunospecifically binds to a RSV antigen of the Group A of RSV. In other embodiments, the anti-RSV-antigen antibody immunospecifically binds to a RSV antigen of the Group B of RSV. In other embodiments,
20 the anti-RSV antigen antibody immunospecifically binds to an antigen of RSV of one Group and cross reacts with the analogous antigen of the other Group. In particular embodiments, the anti-RSV-antigen antibody immunospecifically binds to a RSV nucleoprotein, RSV phosphoprotein, RSV matrix protein, RSV small hydrophobic protein, RSV RNA-dependent RNA polymerase, RSV F protein, and/or RSV G protein. In
25 additional specific embodiments, the anti-RSV-antigen antibody binds to allelic variants of a RSV nucleoprotein, a RSV nucleocapsid protein, a RSV phosphoprotein, a RSV matrix protein, a RSV attachment glycoprotein, a RSV fusion glycoprotein, a RSV nucleocapsid protein, a RSV matrix protein, a RSV small hydrophobic protein, a RSV RNA-dependent RNA polymerase, a RSV F protein, a RSV L protein, a RSV P protein, and/or a RSV G
30 protein.

Anti-viral therapies and their dosages, routes of administration and recommended usage are known in the art and have been described in such literature as the *Physician's Desk Reference* (57th ed., 2003). Additional information on respiratory viral infections is available in *Cecil Textbook of Medicine* (18th ed., 1988).

663-64

5.7 Methods of Administering the SYNAGIS® Formulations

The invention provides methods of treatment, prophylaxis, and amelioration of a RSV infection or one or more symptoms thereof by administering to a subject of an effective amount of liquid formulations of the invention. The subject is preferably a mammal such as non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey such as a cynomolgous monkey and a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely.

Various delivery systems are known and can be used to administer a liquid formulation of the present invention. Methods of administering SYNAGIS® liquid formulations of the present invention include, but are not limited to, parenteral administration (e.g., intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural administration, topical administration, pulmonary administration, and mucosal administration (e.g., intranasal and oral routes). In a specific embodiment, liquid formulations of the present invention are administered intramuscularly, intravenously, or subcutaneously and, preferably, intramuscularly. The formulations may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can be employed, e.g., by use of an inhaler or nebulizer.

The invention also provides that a liquid formulation of the present invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of the SYNAGIS® or antigen-binding fragments thereof. Preferably, the liquid formulations of the present invention are in a hermetically sealed container indicating the quantity and concentration of the antibody or antibody fragment. Preferably, the liquid formulation of the present invention is supplied in a hermetically sealed container at least 15 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml, 150 mg/ml, 200 mg/ml, 250 mg/ml, or 300 mg/ml and, most preferably, 105 mg/ml, in a quantity of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml and, most preferably, 1.2 ml.

The amount of the liquid formulations of the present invention which will be effective in the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof can be determined by standard clinical techniques. For

WO 03/105894

PCT/US03/18913

example, the dosage of the composition which will be effective in the treatment, prevention or amelioration of symptoms associated with a RSV infection can be determined by administering the formulation to a cotton rat, measuring the RSV titer after challenging the cotton rat with 10^5 pfu of RSV and comparing the RSV titer to that obtain for a cotton rat not administered the formulation. Accordingly, a dosage that results in a 2 log decrease or a 99% reduction in RSV titer in the cotton rat challenged with 10^5 pfu of RSV relative to the cotton rat challenged with 10^5 pfu of RSV but not administered the formulation is the dosage of the formulation that can be administered to a human for prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof. The dosage of the formulation which will be effective in prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof can be determined by administering the formulation to an animal model (e.g., a cotton rat or monkey) and measuring the serum titer of SYNAGIS® or antigen-binding fragments thereof. Accordingly, a dosage of the formulation that results in a serum titer of at least 1 µg/ml, preferably 2 µg/ml, 5 µg/ml, 10 µg/ml, 20 µg/ml, 25 µg/ml, at least 35 µg/ml, at least 40 µg/ml, at least 50 µg/ml, at least 75 µg/ml, at least 100 µg/ml, at least 125 µg/ml, at least 150 µg/ml, at least 200 µg/ml, at least 250 µg/ml, at least 300 µg/ml, at least 350 µg/ml, at least 400 µg/ml, or at least 450 µg/ml can be administered to a human for prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges.

The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the RSV infection, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model (e.g., the cotton rat or Cynomolgous monkey) test systems.

For antibodies (e.g., SYNAGIS®), proteins, polypeptides, peptides and fusion proteins, the dosage administered to a patient is typically about 1 mg/kg to 30 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 10 mg/kg and 20 mg/kg of the patient's body weight, more preferably 15 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage, volume and frequency of administration of liquid formulations of the

present invention may be reduced by increasing the concentration of SYNAGIS® or an antigen-binding fragment thereof in the formulations, increasing affinity and/or avidity of SYNAGIS® or an antigen-binding fragment thereof, and/or increasing the half-life of SYNAGIS® or an antigen-binding fragment thereof.

5 Exemplary doses of a small molecule include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

10 In a specific embodiment, a mammal, preferably a human, is administered a stable liquid formulation of the present invention for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective for decreasing RSV titers. In accordance with this embodiment, an effective amount of the liquid formulations of the present invention reduces the RSV titers in the lung as measured,
15 for example, by the concentration of RSV in sputum samples or a lavage from the lungs from a mammal. In another embodiment, a mammal, preferably a human, is administered a liquid formulation of the present invention for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective for inducing an immune response in the mammal.

20 In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulation of the present invention comprising 30 mg/kg or less, 15 mg/kg or less, 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an
25 amount effective to induce a serum titer of at least 1 µg/ml, preferably at least 2 µg/ml, at least 5 µg/ml, at least 10 µg/ml, at least 15 µg/ml, at least 20 µg/ml, at least 25 µg/ml, at least 30 µg/ml, at least 35 µg/ml, at least 40 µg/ml 20 days (preferably 25, 30, 35, 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. In a specific embodiment, a liquid formulation of the present invention comprises
30 SYNAGIS® or an antigen-binding fragment thereof and is administered to a subject a first dose of about 1 mg/kg to about 30 mg/kg to induce a serum titer of about 40 µg/ml or higher 30 days after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said SYNAGIS® or an antigen-binding

fragment thereof is less than 50 µg/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulations of the present invention comprising 30 mg/kg or less, 15 mg/kg or less, 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less or 0.5 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a serum titer of at least 1 µg/ml, preferably at least 2 µg/ml, at least 5 µg/ml, at least 10 µg/ml, at least 15 µg/ml, at least 20 µg/ml, or at least 25 µg/ml 20 days (preferably 25, 30, 35, 40 days) after the administration of the first dose and prior to the administration of subsequent dose. Preferably, the serum titer of said SYNAGIS® or an antigen-binding fragment thereof is less than 30 µg/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulation of the present invention comprising 30 mg/kg or less, 15 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less or 0.5 mg/kg or less of a modified form of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof which has an increased *in vivo* half-life in an amount effective to induce a serum titer of at least 1 µg/ml, preferably at least 2 µg/ml, at least 5 µg/ml, at least 10 µg/ml, at least 15 µg/ml, at least 20 µg/ml, or at least 25 µg/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said SYNAGIS® or an antigen-binding fragment thereof is less than 30 µg/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulation of the present invention comprising 30 mg/kg or less, 15 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less of a modified SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof which has an increased *in vivo* half-life in an amount effective to induce a serum titer of at least 1 µg/ml, preferably at least 2 µg/ml, at least 5 µg/ml, at least 10 µg/ml, at least 15 µg/ml, at least 20 µg/ml, or at least 25 µg/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

Preferably, the serum titer of said SYNAGIS® or an antigen-binding fragment thereof is less than 30 µg/ml 30 days after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of the liquid formulation comprising approximately 30 mg/kg or less, 15 mg/kg or less (preferably 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less) of a modified form of SYNAGIS® or an antigen-binding fragment thereof which has an increased *in vivo* half-life for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a serum titer of at least 30 µg/ml, preferably at least 35 µg/ml, at least 40 µg/ml, or at least 50 µg/ml 25 days (preferably 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose.

In one embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulation of the present invention for pulmonary delivery comprising 30 mg/kg or less, 15 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, 0.5 mg/kg or less, or 0.01 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a titer of at least 20 ng per mg of lung protein (preferably at least 40 ng/mg, at least 60 ng/mg, at least 80 ng/mg, at least 50 ng/mg, at least 75 ng/mg, at least 100 ng/mg, or at least 150 ng/mg) in an intubation sample or lavage from the lungs of said mammal 20 days (preferably 25, 30, 35, or 40 days) after the administration of the first dose and prior to the administration of a subsequent dose. Preferably, the serum titer of said SYNAGIS® or an antigen-binding fragment thereof is less than 100 ng/ml of protein 30 days after the administration of the first dose and prior to the administration of a subsequent dose.

In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid formulation of the present invention 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a serum titer of at least 35 µg/ml, at least 40 µg/ml, at least 50 µg/ml, at least 80 µg/ml, at least 100 µg/ml, at least 120 µg/ml, at least 150 µg/ml, at least 200 µg/ml, at least 250 µg/ml, or at least 300 µg/ml 20 days (preferably 25, 30, 35 or 40 days) after the administration of the first dose. In another embodiment, a mammal, preferably a human, is administered a first dose of a liquid

WO 03/105894

PCT/US03/18913

formulation of the present invention comprising approximately 15 mg/kg of SYNAGIS® or an antigen-binding fragment thereof for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a serum titer of at least 100 µg/ml, at least 125 µg/ml, at least 150 µg/ml, at least 200 µg/ml, at least 250 µg/ml, at least 300 µg/ml, at least 350 µg/ml, at least 400 µg/ml, or at least 450 µg/ml 20 days (preferably 25, 30, 35 or 40 days) after the administration of the first dose. The term "approximately 15 mg/kg" as used herein refers to a range of between 14 mg/kg and 16 mg/kg.

In another embodiment, a mammal, preferably a human, is administered a dose of a liquid formulation of the present invention comprising SYNAGIS® or an antigen-binding fragment thereof for the prevention of a RSV infection or a symptom thereof in an amount effective to induce a prophylactically effective serum titer of less than 10 µg/ml, less than 8 µg/ml, less than 5 µg/ml, less than 3 µg/ml, less than 1 µg/ml, or less than 0.5 µg/ml 30 days after the administration of the dose, wherein said prophylactically effective serum titer is the serum titer that reduces the incidence of RSV infection in the human or the serum titer in a cotton rat that results in a RSV titer 5 days after challenge with 10⁵ pfu RSV that is 99% lower than the RSV titer in the cotton rat 5 days after challenge with 10⁵ pfu of RSV in a cotton rat not administered the dose prior to challenge. Preferably, the dose of the therapeutic or pharmaceutical composition comprises 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less of SYNAGIS® or an antigen-binding fragment thereof.

In yet another embodiment, a mammal, preferably a human, is administered a dose of a liquid formulation of the present invention comprising SYNAGIS® or an antigen-binding fragment thereof for the treatment, management or amelioration of a RSV infection or one or more symptoms thereof in an amount effective to induce a therapeutically effective serum titer of less than 10 µg/ml, less than 8 µg/ml, less than 5 µg/ml, less than 3 µg/ml, less than 1 µg/ml, or less than 0.5 µg/ml 30 days after the administration of the dose, wherein said therapeutically effective serum titer is the serum titer that reduces the severity or length of RSV infection or is the serum titer in a cotton rat that results in a RSV titer in the rat 5 days after challenge with 10⁵ pfu RSV that is 99% lower than the RSV titer 5 days after challenge with 10⁵ pfu of RSV in a cotton rat not administered the dose prior to challenge. Preferably, the dose of the liquid formulation of the present invention comprises 12 mg/kg or less, 10 mg/kg or less, 5 mg/kg or less, 3 mg/kg or less, 1 mg/kg or less, or 0.5 mg/kg or less of an antibody or an antigen-binding fragment thereof.

In a specific embodiment, formulations of the present invention are administered once a month just prior to or during the RSV season. In another embodiment, the formulations are administered every two months just prior to or during the RSV season. In yet another embodiment, the stable formulations of the present invention are administered once just prior to or during the RSV season. The term "RSV season" refers to the season when RSV infection is most likely to occur. Typically, the RSV season in the northern hemisphere commences in November and lasts through April.

In one embodiment, a liquid formulation comprising approximately 5 mg/kg or less (preferably 1.5 mg/kg or less) of SYNAGIS® or an antigen-binding fragment thereof is administered five times, 3 times, or 1 to 2 times during a RSV season to a mammal, preferably a human. In another embodiment, approximately 1.5 mg/kg of SYNAGIS® or an antigen-binding fragment thereof, in the liquid formulations of the present invention is administered monthly five times during a RSV season to a mammal, preferably a human, intramuscularly. In another embodiment, 3 mg/kg of SYNAGIS® or an antigen-binding fragment thereof in the liquid formulation of the invention is administered monthly three times during a RSV season to a mammal, preferably a human, intramuscularly. In yet another embodiment, 5 mg/kg of an SYNAGIS® or an antigen-binding fragment thereof in a liquid formulation of the invention is administered monthly one to two times during a RSV season to a mammal, preferably a human, intramuscularly.

In a specific embodiment, 15 mg/kg of SYNAGIS® or an antigen-binding fragment thereof in the liquid formulation of the present invention is administered to a mammal, preferably a human, intramuscularly five times during a RSV season, wherein said SYNAGIS® or antibody fragment has an increased *in vivo* half-life. In another embodiment, approximately 5 mg/kg or less (preferably 1.5 mg/kg or less) of SYNAGIS® or an antigen-binding fragment thereof in the liquid formulation of the present invention is administered five times, 3 times, or 1 to 2 times during a RSV season to a mammal, preferably a human. In another embodiment, 3 mg/kg of SYNAGIS® or an antigen binding fragment thereof, which has an increased *in vivo* half-life, in the liquid formulation of the present invention is administered monthly three times during a RSV season to a mammal, preferably a human, intramuscularly. In another embodiment, 5 mg/kg of SYNAGIS® or an antigen-binding fragment thereof, which has an increased *in vivo* half life, in the liquid formulation of the present invention is administered to a mammal, preferably a human, intramuscularly twice times during a RSV season.

5.8 Biological Assays

5.8.1 Immunospecificity of the Antibodies of the Invention

Antibodies of the present invention or fragments thereof may be characterized in a variety of ways well-known to one of skill in the art. In particular, antibodies of the invention or antigen-binding fragments thereof in a liquid formulation of the present
5 invention may be assayed for the ability to immunospecifically bind to an epitope of a respiratory syncytial virus. Such an assay may be performed in solution (e.g., Houghten, 1992, *Bio/Techniques* 13:412-421), on beads (Lam, 1991, *Nature* 354:82-84), on chips (Fodor, 1993, *Nature* 364:555-556), on bacteria (U.S. Patent No. 5,223,409), on spores (U.S. Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (Cull *et al.*, 1992,
10 *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici, 1991, *J. Mol. Biol.* 222:301-310) (each of these references is incorporated herein in its entirety by reference). SYNAGIS® or an antigen-binding fragment thereof in a liquid
15 formulation of the present invention can be assayed for its specificity and affinity.

SYNAGIS® or an antigen-binding fragment thereof of the present invention may be assayed for immunospecific binding to a RSV antigen and cross-reactivity with other antigens by any method known in the art. Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and
20 non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name
25 but a few. Such assays are routine and well-known in the art (see, e.g., Ausubel *et al.*, eds., 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety).

5.8.2 *In vitro* and *in vivo* Assays

A liquid formulation or a combination therapy of the present invention can be tested
30 *in vitro* and/or *in vivo* in various assays or suitable animal model systems for its activity.

A liquid formulation of the present invention for treating, managing, preventing, or ameliorating a RSV infection or one or more symptoms thereof can be tested for its ability to inhibit viral replication or reduce viral load in *in vitro* assays. For example, viral

replication can be assayed by a plaque assay such as described, *e.g.*, by Johnson *et al.*, 1997, Journal of Infectious Diseases 176:1215-1224 176:1215-1224. A liquid formulation of the invention administered according to the methods of the invention can also be assayed for their ability to inhibit or down-regulate the expression of viral polypeptides. Techniques
5 known to those of skill in the art, including, but not limited to, western blot analysis, northern blot analysis, and RT-PCR can be used to measure the expression of viral polypeptides and/or viral titers.

A liquid formulation of the invention can be tested in suitable animal model systems prior to use in humans. Such animal model systems include, but are not limited to, rats,
10 mice, chicken, cows, monkeys, pigs, dogs, rabbits, etc. Any animal system well-known in the art may be used. Several aspects of the procedure may vary; said aspects include, but are not limited to, the temporal regime of administering the therapies (*e.g.*, prophylactic and/or therapeutic agents) whether such therapies are administered separately or as an admixture, and the frequency of administration of the therapies.

15 Animal models can be used to assess the efficacy of the methods of the invention for treating, managing, preventing, or ameliorating a RSV infection or one or more symptom thereof. Animal models for RSV infection include, but are not limited to, those as described by, *e.g.*, Piedimonte *et al.*, Am J Physiol 1999, 277:L831-L840; McArthur-Vaughan *et al.*, J. Med. Primatol. 2002, 31(2):61-73; and Byrd *et al.*, Clin. Infect. Dis. 1997, 25(6):1363-8.
20 In a specific embodiment, cotton rats are administered a liquid formulation comprising SYNAGIS® according to the methods of the invention, challenged with 10^5 pfu of RSV, and four or more days later, the rats are sacrificed and RSV titer and SYNAGIS® serum titer is determined. Accordingly, a dosage that results in a 2 log decrease or a 99% reduction in RSV titer in the cotton rat challenged with 10^5 pfu of RSV relative to the cotton rat
25 challenged with 10^5 pfu of RSV but not administered the formulation is the dosage of the formulation that can be administered to a human for the treatment, prevention or amelioration of a RSV infection or one or more symptoms thereof. Further, this embodiment, the tissues (*e.g.*, the lung tissues) from the sacrificed rats can be examined for histological changes.

30 The administration of a liquid formulation of the invention according to the methods of the present invention can be tested for its ability to decrease the time course of a RSV infection by at least 25%, preferably at least 50%, at least 60%, at least 75%, at least 85%, at least 95%, or at least 99%. A liquid formulation of the invention can also be tested for its ability to increase the survival period of humans suffering from a RSV infection by at least

672 #3

25%, preferably at least 50%, at least 60%, at least 75%, at least 85%, at least 95%, or at least 99%. Further, a liquid formulation of the invention can be tested for its ability to reduce the hospitalization period of a human suffering from RSV infection by at least 60%, preferably at least 75%, at least 85%, at least 95%, or at least 99%. Techniques known to those of skill in the art can be used to analyze the function of a liquid formulation of the invention *in vivo*.

Further, any *in vitro* or *in vivo* assays known to those skilled in the art can be used to evaluate the prophylactic and/or therapeutic utility of a liquid formulation of the invention disclosed herein for a RSV infection or one or more symptoms thereof.

5.8.3 Toxicity Assays

The toxicity and/or efficacy of the prophylactic and/or therapeutic compounds of the invention can be determined by standard pharmaceutical practices in cell culture or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Therapies that exhibit large therapeutic indices are preferred. While therapies that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

2 The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the prophylactic and/or therapeutic agents for use in humans. The dosage of such agents lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any therapy used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be determined in animal models to achieve a circulating plasma concentration range that includes the ED50 (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

5.9 Kits

673 74

674/5

The invention provides a pharmaceutical pack or kit comprising one or more containers filled with a liquid formulation of the invention for the prevention, treatment, management or amelioration of a RSV infection or one or more symptoms thereof. In a specific embodiment, the liquid formulations of the invention comprise SYNAGIS® or an antigen-binding fragment thereof recombinantly fused or chemically conjugated to another moiety, including but not limited to, a heterologous protein, a heterologous polypeptide, a heterologous peptide, a large molecule, a small molecule, a marker sequence, a diagnostic or detectable agent, a therapeutic moiety, a drug moiety, a radioactive metal ion, a second antibody, and a solid support.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises a liquid formulation of the invention, in one or more containers. In another embodiment, a kit comprises a liquid formulation of the invention, in one or more containers, and one or more other prophylactic or therapeutic agents useful for the prevention, management or treatment of a RSV infection or one or more symptoms thereof, in one or more other containers. Preferably, the kit further comprises instructions for preventing, treating, managing or ameliorating a RSV infection (e.g., using the liquid formulations of the invention alone or in combination with another prophylactic or therapeutic agent), as well as side effects and dosage information for method of administration. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

6. EXAMPLES

6.1 Example 1 (Stability Study)

An antibody formulation of the present invention comprising, in an aqueous carrier, 25 mM of histidine, 1.6 mM of glycine, and SYNAGIS® at pH 6 was prepared according to the following protocol:

For a 1 kg solution of buffer: In 800 g water, 3.875 g histidine (free base) and 0.12 g glycine were dissolved. The pH was adjusted with 6 N HCl to 6.0 ± 0.2. Water was added to bring the total mass up to 1.0 kg (qs).

For the diafiltration: After the chromatography steps in the purification process, SYNAGIS® was concentrated to a target of 150 g/L. The concentrated product is diafiltered

into formulation buffer. The formulated product was diluted to a target manufacturing concentration of 103 ± 3 g/L.

For a stability study, two formulations were prepared: one contained 105 mg/ml of SYNAGIS[®] and the other contained 160 mg/ml of SYNAGIS[®]. The stability of each formulation was measured using HPSEC in terms of degrees of aggregate formation and fragmentation during the storage at 2-8°C for up to 15 months and at 38-42°C for up to 1 year. For the HPSEC analysis, typically, TosohHaas G3000WXL column with a mobile phase containing 0.1 M sodium phosphate and 0.1 M sodium sulfate, pH 6.8, is used at a flow rate of 0.8 ml/min. A sample containing 250 mg of protein in an appropriate volume is injected into the column and protein peaks are detected by 280 nm UV and/or fluorescence (280 nm excitation and 340 nm emission).

The data showed that there was no detectable increase in aggregation when each formulation of SYNAGIS[®] was stored at 2-8°C for 15 months as shown in Table 3.

Table 3. Percent Aggregates during Storage at 2-8°C.

Month	% Aggregates	
	105 mg/ml	160 mg/ml
0	0.3	0.4
5	0.3	0.3
8	0.4	---
12	0.4	---
15	0.4	0.5

± 0.1% error.

When the formulations were stored at 38-42°C for 60 days, about 1.5% increase in aggregate was observed with the formulation containing 105 mg/ml of SYNAGIS[®] and 2.0% increase was observed with the formulation containing 160 mg/ml of SYNAGIS[®].

5.2 Example 2 (Clinical Study)

The liquid formulation of the present invention comprising 100 mg/ml of SYNAGIS[®] in an aqueous solution containing 25 mM of histidine and 1.6 mM of glycine at pH 6 is tested for safety and tolerability study in a Phase I, parallel group, double-blind, randomized study at two sites. The study drugs are a liquid (Liq) formulation of

SYNAGIS[®] and the currently licensed lyophilized (Lyo) formulation of SYNAGIS[®]. A total of 48 volunteers will be randomized to one of four treatment groups:

GROUP 1:	N=12	3 mg/kg SYNAGIS [®] (Liq) at Study Days 0 and 30 (IM)
GROUP 2:	N=12	3 mg/kg SYNAGIS [®] (Lyo) at Study Days 0 and 30 (IM)
GROUP 3:	N=12	15 mg/kg SYNAGIS [®] (Liq) at Study Day 0 (IV)
GROUP 4:	N=12	15 mg/kg SYNAGIS [®] (Lyo) at Study Day 0 (IV)

Vital signs will be obtained before and 30 minutes after each dose of study drug. Adverse events will be monitored through 30 days after the last dose of study drug and serious adverse events will be monitored through Study Day 60.

10 On Study Day 0, all volunteers will have blood collected for SYNAGIS[®] serum concentration before dosing, at the end of infusion (IV dose groups only), and at 0.25, 0.5, 1, 4, 8, and 12 hours after IM injection or end of infusion. Subsequently, blood samples for determination of SYNAGIS[®] levels will be collected daily through Study Day 5 and on Study Days 7, 14, 21, 30, 37 (IM groups only), and 60. Serum samples for anti-SYNAGIS[®] antibodies will be collected on Study Days 0, 7, 14, 21, 30, 37 (IM groups only), and 60. Samples for serum chemistry and CBC with differential and platelets, and urine samples for urinalysis will be collected on Study Day 0 as well as 7 days after each dose of SYNAGIS[®] (Study Day 7 for the IV groups and Study Days 7 and 37 for the IM groups). Urine β HCG tests will be performed on the day of dosing before each dose of SYNAGIS[®] (Study Day 0 for the IV groups and Study Days 0 and 30 for the IM groups). A study flow diagram is shown in Fig. 2.

6.2.1 Study procedures

A. Volunteer Selection

25 The volunteers in this study will be healthy male or female adults. The volunteer will be counseled by an investigator (physician) who will address the questions and concerns of the volunteer and secure written informed consent for participation in the study. Written informed consent will be obtained prior to conducting study procedures or administration of study drug.

a. Inclusion Criteria

30 Volunteers must meet *all* of the following criteria:

1. Male or female.
2. Age 18 through 49 years at the time of the first dose of study drug.

667 70
677

3. Weight ≤ 150 kg.
4. Written informed consent obtained from the volunteer.
5. Sexually active females, unless surgically sterile, must have used an effective method of avoiding pregnancy (including oral or implanted contraceptives, IUD, female condom, diaphragm with spermicide, cervical cap, abstinence, use of a condom by the sexual partner or sterile sexual partner) for 14 days prior to the first dose of study drug, must agree to continue using such precautions for 30 days after the final dose of study drug, and must have a negative serum pregnancy test within 2 days prior to the first dose of study drug.
- 10 6. Healthy by medical history and physical examination.
7. Ability to complete follow-up period of 60 days as required by the protocol.

b. Exclusion Criteria

Volunteers must have *none* of the following:

1. Acute illness at the start of the study
- 15 2. Fever $\geq 99.5^{\circ}\text{F}$ at the start of the study
3. Any drug therapy within 7 days prior to Study Day 0 (except for contraceptives)
4. Blood donation in excess of 400 mL within 6 months of study start
5. Receipt of immunoglobulin or blood products within 60 days before entry into the study
- 20 6. Receipt of any investigational drug therapy or standard vaccine within 120 days before the first dose of study drug in this protocol through 60 days after the final dose of study drug
7. History of immunodeficiency
8. History of allergic disease or reactions likely to be exacerbated by any
- 25 component of the study drug
9. Previous medical history or evidence of an intercurrent illness that may compromise the safety of the volunteer in the study
10. Evidence of infection with hepatitis A, B, or C virus or HIV-1
11. At screening (must be within 21 days before entry into the study) any of the
- 30 following: CBC: Hgb < 12.0 gm/dl; WBC $< 4,000/\text{mm}^3$; platelet count $< 120,000/\text{mm}^3$ (or laboratory normal values); AST, ALT, BUN, creatinine $>$ upper limit of normal; other abnormal laboratory values in the screening panel which in the opinion of the principal investigator are judged to be clinically significant; other abnormal laboratory values in the

screening panel which in the opinion of the principal investigator are judged to potentially confound analysis of study results

12. Nursing mother

13. History of alcohol or drug abuse within the past 2 years

14. Evidence of any systemic disease on physical examination

B. Randomization

a. Volunteer Randomization Procedures and Treatment Allocation

At the screening visit, volunteers will be evaluated by the principal investigator to assess eligibility for entry into the study. A master log will be maintained for all screened volunteers. Volunteers who sign an informed consent and who meet eligibility criteria will be entered into the study. When a volunteer arrives in the study site for randomization (Study Day 0), the investigator will confirm that the volunteer meets all inclusion and exclusion criteria. The investigator will then assign a patient identification number (PID). Patient identification numbers will be assigned sequentially within each of the two study sites beginning with #101 in site 1 and with #201 in site 2. Volunteers will be considered to have entered the study when the PID is assigned. A randomization list provided to the study pharmacist at each study site will contain assignments to each of the four treatment groups for volunteers at that site. The investigator will notify MedImmune by facsimile transmission (fax) at 301-527-4217 that a volunteer has been randomized. Volunteers who have been assigned a PID and do not receive any study drug, who receive an incomplete infusion of study drug, who do not receive both IM injections of study drug, or who do not complete at least 50% of the study visits may be replaced at the discretion of the sponsor. Volunteers who withdraw due to an adverse event or whose status cannot be ascertained will not be replaced. Volunteers who withdraw consent for reasons other than an adverse event may be replaced. Replacement volunteers will be assigned a new PID. Volunteers who are replaced will continue to be followed for safety according to the protocol

b. Blinding

This is a double-blind study. Blinding will be maintained for assignment of volunteers to lyophilized or liquid formulation within IM or IV groups. In order to maintain blinding during administration of the two formulations of SYNAGIS®, the study pharmacist at each site will prepare the study drug at a site physically removed from the treatment station and shielded from the observation of the principal investigator or any study personnel directly involved in the conduct of the study. For IM injection, the pharmacist

will prepare identical appearing 5 mL syringes containing the calculated volume of either liquid or reconstituted lyophilized SYNAGIS®. For IV infusion, the pharmacist will prepare identical appearing 200 mL infusion bags containing the calculated volume of either liquid or reconstituted lyophilized SYNAGIS®. Labels will not identify whether the syringe/bag contains liquid or reconstituted lyophilized SYNAGIS®. An independent monitor who will review the pharmacy record only, the statistician and clinical supplies manager at MedImmune, and the study pharmacist at the study site are the only individuals who will have access to the randomization list which identifies a volunteer's study treatment allocation. These individuals must not reveal randomization information to anyone. In the event that the study treatment for a volunteer becomes known to the investigator, MedImmune must be notified immediately by the investigator. All instances of unblinding will be documented in the study report.

C. Study Drug

a. Study Drug Supplies and Accountability

The sponsor will provide the investigator with adequate quantities of liquid SYNAGIS®, lyophilized SYNAGIS®, and diluent (sterile water for injection). Study drug should be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Liquid SYNAGIS® will be provided in 3 mL vials containing 100 mg of sterile liquid product in a volume of 1 mL (25 mM histidine, 1.6 mM glycine, at pH 6.0).

Lyophilized SYNAGIS® will be provided in 5 mL vials containing 100 mg of sterile lyophilized product which when formulated (before lyophilization) contains 25 mM histidine, 1.6 mM glycine, and 3% (w/v) mannitol at pH 6.0.

The study pharmacist is required to maintain accurate drug accountability records. Upon completion of the study, all study drug accountability records will be returned to the sponsor. All unused study drug will be returned to the sponsor.

b. Treatment Regimens

The following regimens are employed in the study:

GROUP 1:	N=12	3 mg/kg SYNAGIS® (Liq) at Study Days 0 and 30 (IM)
GROUP 2:	N=12	3 mg/kg SYNAGIS® (Lyo) at Study Days 0 and 30 (IM)
GROUP 3:	N=12	15 mg/kg SYNAGIS® (Liq) at Study Day 0 (IV)
GROUP 4:	N=12	15 mg/kg SYNAGIS® (Lyo) at Study Day 0 (IV)

a. Ordering and Preparation of Study Drug

The dose of study drug for administration must be prepared by the study pharmacist. The study drug prescription form indicating the PID and the volunteer's body weight will be sent to the pharmacist by the investigator (or designee). The study pharmacist will then use this information to prepare the study drug.

To prepare liquid or lyophilized SYNAGIS[®] for administration, the pharmacist should remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent. The vial should be vented. Doses for each volunteer will be calculated as described below based on the volunteer's weight (to the nearest 0.1 kilogram) on the day SYNAGIS[®] is administered. The dose should be rounded to the nearest 0.1 mL. All preparations of study drug must be administered within 6 hours after entering the vial of SYNAGIS[®]. If it is not administered within 6 hours a new vial or vials must be used.

Preparation of Liquid SYNAGIS[®]

(1) For IM injections: The required volume of liquid SYNAGIS[®] (100 mg/mL) will be obtained by pooling the contents of as many vials as necessary with a 5 mL syringe.

$$\text{Dose (mL)} = [\text{Volunteer Weight (kg)} \times \text{Dose Level (3 mg/kg)}] \div \text{Drug Concentration (100 mg/mL)}$$

Example: A volunteer who weighs 75.6 kg receives 2.3 mL of SYNAGIS[®]

$$(75.6 \text{ kg} \times 3 \text{ mg/kg}) \div 100 \text{ mg/mL} = 2.268 \text{ mL (rounded to 2.3 mL)}$$

(2) For IV infusions: The required volume of liquid SYNAGIS[®] (100 mg/mL) will be obtained by pooling the contents of as many vials as necessary with a 20 mL (or larger) syringe.

$$\text{Dose (mL)} = [\text{Volunteer Weight (kg)} \times \text{Dose Level (15 mg/kg)}] \div \text{Drug Concentration (100 mg/mL)}$$

This volume of liquid SYNAGIS[®] will then be injected into an empty 200 mL infusion bag and diluted with diluent 1:4 by adding four volumes of diluent to the bag for a final concentration of 20 mg/mL SYNAGIS[®].

Example: A volunteer who weighs 71.4 kg receives 10.7 mL of SYNAGIS[®]

$$[(71.4 \text{ kg} \times 15 \text{ mg/kg}) \div 100 \text{ mg/mL} = 10.71 \text{ mL (rounded to 10.7 mL)}]$$

and 42.8 mL of diluent (4 x 10.7) for a total infusion volume of 53.5 mL.

Preparation of Lyophilized SYNAGIS[®]

(2) For IM injections: One (1) ml of diluent should be added slowly to the vial of lyophilized SYNAGIS® for a final concentration of 100 mg/mL SYNAGIS®. The vial should then be gently swirled for 30 seconds to avoid foaming. Reconstituted SYNAGIS® should stand at room temperature for a minimum of 20 minutes until SYNAGIS® clarifies.

The required volume of reconstituted lyophilized SYNAGIS® (100 mg/mL) will be obtained by pooling the contents of as many vials as necessary with a 5 mL syringe.

$$\text{Dose (mL)} = [\text{Volunteer Weight (kg)} \times \text{Dose Level (3 mg/kg)}] \div \text{Drug Concentration (100 mg/mL)}$$

Example: A volunteer who weighs 75.6 kg receives 2.3 mL of SYNAGIS®

10 $(75.6 \text{ kg} \times 3 \text{ mg/kg}) \div 100 \text{ mg/mL} = 2.268 \text{ mL (rounded to 2.3 mL)}$

(2) For IV infusions: Five (5) ml of diluent should be added slowly to the vial of lyophilized SYNAGIS® for a final concentration of 20 mg/mL SYNAGIS®. The vial should then be gently swirled for 30 seconds to avoid foaming. Reconstituted SYNAGIS® should stand at room temperature for a minimum of 20 minutes until SYNAGIS® clarifies.

15 The required volume of reconstituted lyophilized SYNAGIS® (20 mg/mL) will be obtained by pooling the contents of as many vials as necessary with a 20 mL (or larger) syringe and injecting this volume into an empty 200 mL infusion bag.

$$\text{Dose (mL)} = [\text{Volunteer Weight (kg)} \times \text{Dose Level (15 mg/kg)}] \div \text{Drug Concentration (20 mg/mL)}$$

20 *Example: A volunteer who weighs 71.4 kg receives 53.6 mL of SYNAGIS®*

$$(71.4 \text{ kg} \times 15 \text{ mg/kg}) \div 20 \text{ mg/mL} = 53.55 \text{ mL (rounded to 53.6 mL)}$$

d. Administration of Study Drug

Study drug for the IM and IV treatment groups will be dispensed from the pharmacy in identical appearing 5 mL syringes and identical appearing 200 mL infusion bags,

25 respectively.

IM Injection

The study drug will be administered by IM injection into the deltoid muscle (after confirming the needle is not in a blood vessel) using standard aseptic technique. Volunteers will remain under observation in the study site for at least 30 minutes after the injection.

30 IV Infusion

Prior to drug administration, an IV catheter will be placed in an accessible vein using standard insertion techniques. Patency of the IV catheter will be maintained by a

continuous IV infusion of 5% Dextrose for Injection USP at a rate of 10 to 25 mL/h. The dextrose infusion will be interrupted, and SYNAGIS® will be infused through a low protein binding 0.22 µm filter at a rate of approximately 1-2 mL/minute. After SYNAGIS® has been administered, the IV tubing should be flushed and kept open with 5% Dextrose for injection USP at 10 to 25 mL/h until the IV catheter is removed.

e. **Concomitant Medications**

All concomitant medications used by the volunteer from Study Day 0 through Study Day 60 will be recorded on the case report form. Volunteers may not receive the following:

1. Immunosuppressive medication (inhaled and topical corticosteroids are permitted).
2. Investigational agents from 120 days before study entry through Study Day 60.

The sponsor must be notified if any volunteer receives prohibited concomitant medications. Volunteers may receive medications to treat adverse events as deemed necessary by the investigator or the volunteer's physician.

D. **Schedule of Volunteer Evaluations**

All volunteers who are assigned a PID and receive any study drug will be followed according to the protocol regardless of the number of doses of study drug received, unless consent for follow-up is withdrawn. The sponsor must be notified of all deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule.

Volunteers will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator. A schedule of screening and on-study visit procedures is presented in Table 4, followed by a detailed description of each visit.

Table 4 Schedule of Volunteer Evaluations

	Scn	Study Day												
		0	1	2	3	4	5	7	14	21	30	37	60	
Written Informed Consent	x													
Verify Eligibility Criteria	x	x												
Medical History	x													
Physical Examination	x													
Height and body weight ^a	x	x									x ^d			
Urinalysis	x	x						X				x ^d		
Hepatitis A, B, C	x													
Serum β HCG ^b	x													
Urine β HCG ^b		x									x ^d			
Serum Chemistry ^c	x	x						X				x ^d		
CBC, Differential, Platelets	x	x						X				x ^d		
SYNAGIS [®] Serum Level		x ^a	x	x	x	x	x	X	x	x	x	x ^d	x	
Anti-SYNAGIS [®] Antibody		x						X	x	x	x	x ^d	x	
Vital Signs ^e		x										x ^d		
Randomization/Assignment of PID		x												
Study Drug Injection (IM Groups)		x										x ^d		
Study Drug Infusion (IV Groups)		x												
Assessment of Adverse Events ^f		x	x	x	x	x	x	X	x	x	x	x ^u	x	

683
84

- a. Blood will be sampled for SYNAGIS® serum concentration before dosing, at the end of infusion (IV dose groups only), and at 0.25, 0.5, 1, 4, 8, and 12 hours after injection/end of infusion.
- b. Females only.
- 5 c. ALT, AST, BUN, Creatinine.
- d. IM dose groups only.
- e. Vital signs obtained before and 30 minutes after each dose.
- f. Adverse events through 30 days after each dose. Serious adverse events through Study Day 60.
- 10 g. Body weight only at Study Day 30.

2. Screening

Note: All screening laboratory assessments must be performed within 21 days before study entry (Study Day 0). The screening evaluations may be carried out over more than one visit.

- 15 1. Written informed consent
2. Verify eligibility criteria
3. Screening medical history
4. Screening physical examination
5. Height and body weight
- 20 6. Urinalysis
7. Blood collection for screening
 - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
 - Serum β HCG (female volunteers only)
 - 25 • Chemistry panel (AST, ALT, BUN, creatinine)
 - CBC with differential and platelet count

Study Day 0: Dose 1

Visit 1

- 30 1. Verify eligibility criteria
2. Height and body weight
3. Urinalysis
4. Urine β HCG (female volunteers only)

685 86

5. Baseline blood collection

- Chemistry panel (AST, ALT, BUN, creatinine)
- CBC with differential and platelet count
- Serum for SYNAGIS® level
- Serum for anti-SYNAGIS® antibody

6. Randomization and assignment of PID

7. Vital signs before administration of study drug (temperature, blood pressure, pulse rate, respiratory rate)

Note: All of the above must be completed before administration of study drug.

1. Administration of study drug
2. Monitor vital signs 30 minutes after injection or end of infusion
3. Monitor for adverse events and serious adverse events
4. Post-dose blood collection
 - Serum for SYNAGIS® levels immediately after completion of infusion (IV dose groups only) and at 0.25, 0.5, 1, 4, 8, and 12 hours after injection/end of infusion

Study Day 1: Dose 1 Pharmacokinetic Sampling

Visit 2

1. Post-dose blood collection for 24 hour SYNAGIS® serum level
2. Monitor for adverse events and serious adverse events

Study Day 2: Dose 1 Pharmacokinetic Sampling

Visit 3

1. Post-dose blood collection for 48 hour SYNAGIS® serum level
2. Monitor for adverse events and serious adverse events

Study Day 3: Dose 1 Pharmacokinetic Sampling

Visit 4

1. Post-dose blood collection for 72 hour SYNAGIS® serum level
2. Monitor for adverse events and serious adverse events

Study Day 4: Dose 1 Pharmacokinetic Sampling

Visit 5

686 87

WO 03/105894

PCT/US03/18913

1. Post-dose blood collection for 96 hour SYNAGIS[®] serum level
2. Monitor for adverse events and serious adverse events

Study Day 5: Dose 1 Pharmacokinetic Sampling

Visit 6

1. Post-dose blood collection for 120 hour SYNAGIS[®] serum level
2. Monitor for adverse events and serious adverse events

Study Day 7:

Visit 7

1. Urinalysis
- 10 2. Blood collection
 - Chemistry panel (AST, ALT, BUN, creatinine)
 - CBC with differential and platelet count
 - Serum for SYNAGIS[®] level
 - Serum for anti-SYNAGIS[®] antibody
- 15 3. Monitor for adverse events and serious adverse events

Study Day 14±1:

Visit 8

1. Blood collection
 - Serum for SYNAGIS[®] level
 - 20 • Serum for anti-SYNAGIS[®] antibody
2. Monitor for adverse events and serious adverse events

Study Day 21±1:

Visit 9

1. Blood collection
 - 25 • Serum for SYNAGIS[®] level
 - Serum for anti-SYNAGIS[®] antibody
2. Monitor for adverse events and serious adverse events

Study Day 30±1:

Visit 10

WG 03/105894

PCT/US03/18913

All volunteers

1. Blood collection

- Serum for SYNAGIS® level
- Serum for anti-SYNAGIS® antibody

2. Monitor for adverse events and serious adverse events

Volunteers in IM groups only

3. Body weight

4. Urine β HCG

5. Vital signs before administration of study drug

6. Administration of study drug

7. Monitor vital signs 30 minutes after injection

Study Day 37 $\pm$ 1:**Visit 11**

Volunteers in IM groups only

1. Urinalysis

2. Blood collection

- Chemistry panel (AST, ALT, BUN, creatinine)
- CBC with differential and platelet count
- Serum for SYNAGIS® level
- Serum for anti-SYNAGIS® antibody

3. Monitor for adverse events and serious adverse events

Study Day 60 $\pm$ 2:**Visit 12**

1. Blood collection

- Serum for SYNAGIS® level
- Serum for anti-SYNAGIS antibody

2. Monitor for serious adverse events

E. Volunteer Evaluation Methods**a. Routine Laboratory Evaluations**

Routine laboratory tests during screening and during the study will be performed at each study site's local clinical laboratory. Urine pregnancy tests during the study will be

performed in the study site using a licensed test. Abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours).

b **Pharmacokinetic and Immunologic Evaluations**

SYNAGIS® serum concentration and anti-SYNAGIS® antibodies will be measured
5 by MedImmune, Inc. by ELISA.

F. **Completion of Study and Loss to Follow-up**

Volunteers will be considered to have completed the study if they were followed up through Study Day 60. It should be specified on the case report form whether or not the
10 volunteer completed the study follow-up procedures through Study Day 60. Volunteers will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the volunteer's status at Study Day 60. The investigator should document attempts to re-establish contact with missing volunteers throughout the study period. If contact with a missing volunteer is re-
15 established, follow-up should resume according to the protocol.

Pharmacokinetic and immunologic evaluations will be made based on SYNAGIS® serum concentration and anti-SYNAGIS® antibodies measured by ELISA.

Equivalents

20 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All publications, patents and patent applications mentioned in this specification are
25 herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

30

CLAIMS

WHAT IS CLAIMED IS:

1. A liquid SYNAGIS[®] formulation comprising: (a) at least 15 mg/ml of SYNAGIS[®], or an antigen-binding fragment; and (b) histidine in an aqueous carrier, wherein said formulation is substantially free of surfactant, inorganic salts or other excipients.
2. The formulation of claim 1, wherein the aqueous carrier is distilled water.
3. The formulation of claim 1, wherein the formulation is sterile.
4. The formulation of claim 1, wherein the formulation is homogenous.
5. The formulation of claim 1, wherein the formulation has a pH in the range between about 5.5 to 6.5.
6. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is at a concentration of at least 100 mg/ml.
7. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is at a concentration of at least 110 mg/ml.
8. The formulation of claim 7, wherein said SYNAGIS[®] or antigen-binding fragment thereof is at a concentration of at least 150 mg/ml.
9. The formulation of claim 8, wherein said SYNAGIS[®] or antigen-binding fragment thereof is at a concentration of at least 160 mg/ml.
10. The formulation of claim 1, wherein histidine is at concentration of about 10 to about 30 mM.
11. The formulation of claim 1 further comprising glycine.
12. The formulation of claim 11, wherein glycine is at a concentration of less than 1.0 mM.

13. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is stable at 40°C for at least 100 days as determined by HPSEC.
14. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is stable at about ambient temperature for at least 1 year as determined by HPSEC.
15. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is stable at 4°C for at least 3 years as determined by HPSEC.
16. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is stable at 4°C for 3-5 years as determined by HPSEC.
17. The formulation of claim 1, wherein said SYNAGIS[®] or antigen-binding fragment thereof is stable at 4°C for at least 5 years as determined by HPSEC.
18. The formulation of claim 1, wherein less than 2% of said SYNAGIS[®] or antigen-binding fragment thereof forms an aggregate as measured by HPSEC.
19. The formulation of claim 18, wherein less than 1% of said SYNAGIS[®] or antigen-binding fragment thereof forms an aggregate as measured by HPSEC.
20. The formulation of claim 19, wherein less than 0.5% of said SYNAGIS[®] or antigen-binding fragment thereof forms an aggregate as measured by HPSEC.
21. The formulation of claim 1 further comprising an excipient.
22. The formulation of claim 21, wherein the excipient is a saccharide.
23. The formulation of claim 22, wherein the saccharide is sucrose.
24. The formulation of claim 23, wherein sucrose is at a concentration of about 1% to about 20%.
25. The formulation of claim 21, wherein the excipient is a polyol other than mannitol.

26. The formulation of claim 25, wherein the polyol is polysorbate.
27. The formulation of claim 25, wherein the polyol is Tween, which is at a concentration of about 0.001% to about 1%.
28. The formulation of claim 1 which has been prepared by a process in which, for each step of said process, said SYNAGIS® or an antigen-binding fragment thereof is in an aqueous phase.
29. The formulation of claim 1 which has been prepared by a process that does not have a drying step.
30. The formulation of claim 1 which has been prepared by a process that does not have a lyophilization step.
31. A pharmaceutical unit dosage form suitable for parenteral administration to a human which comprises the formulation of claim 1 or 3 in a suitable container.
32. The pharmaceutical unit dosage form of claim 31, wherein said SYNAGIS® or an antigen-binding fragment thereof has a concentration of from about 15 mg/ml to about 300 mg/ml in a volume of from 1 ml to 20 ml.
33. The pharmaceutical unit dosage form of claim 32, wherein said SYNAGIS® or an antigen-binding fragment thereof has a concentration of 100 mg/ml in a volume of 1.2 ml.
34. The pharmaceutical unit dosage form of claim 32, wherein the formulation is suitable for subcutaneous administration.
35. The pharmaceutical unit dosage form of claim 32, wherein the formulation is suitable for intravenous administration.
36. The pharmaceutical unit dosage form of claim 32, wherein the formulation is suitable for intramuscular administration.
37. A pharmaceutical unit dosage form suitable for aerosol administration to a human which comprises the formulation of claim 1 or 3 in a suitable container.

38. The pharmaceutical unit dosage form of claim 37, wherein said SYNAGIS[®] or an antigen-binding fragment thereof has a concentration of from about 15 mg/ml to about 300 mg/ml in a volume of from 1.1 ml to 1.3 ml.

39. A sealed container comprising the formulation of claim 1, 2 or 3.

40. A method of preventing, treating or ameliorating one or more symptoms associated with a RSV infection in a subject, said method comprising administering a prophylactically or therapeutically effective amount of the formulation of claim 1, 3, 29, 30, or 31.

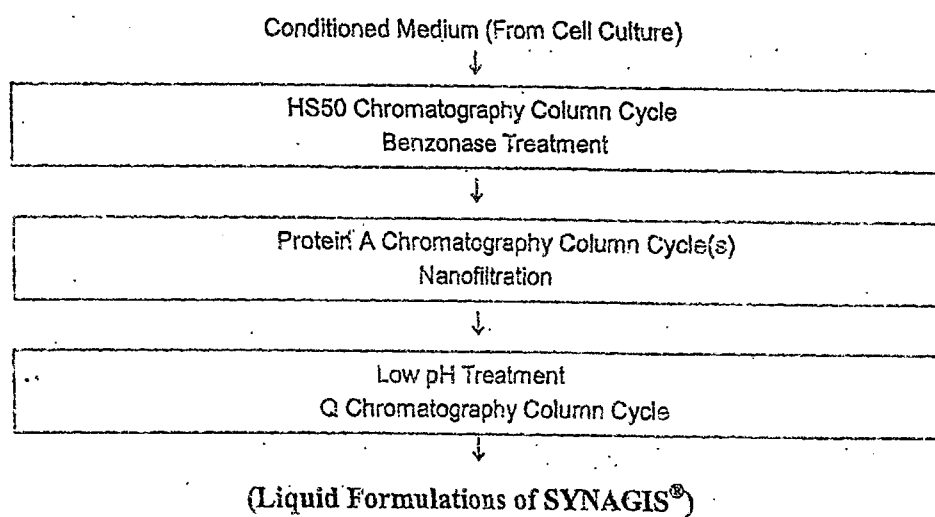
41. The method of claim 40, wherein the formulation is administered parenterally.

42. The method of claim 40, wherein the formulation is administered intramuscularly.

43. The method of claim 40, wherein the formulation is administered intravenously.

44. The method of claim 40, wherein the formulation is administered subcutaneously.

45. The method of claim 40, wherein the formulation is administered intranasally.

**Fig. 1**

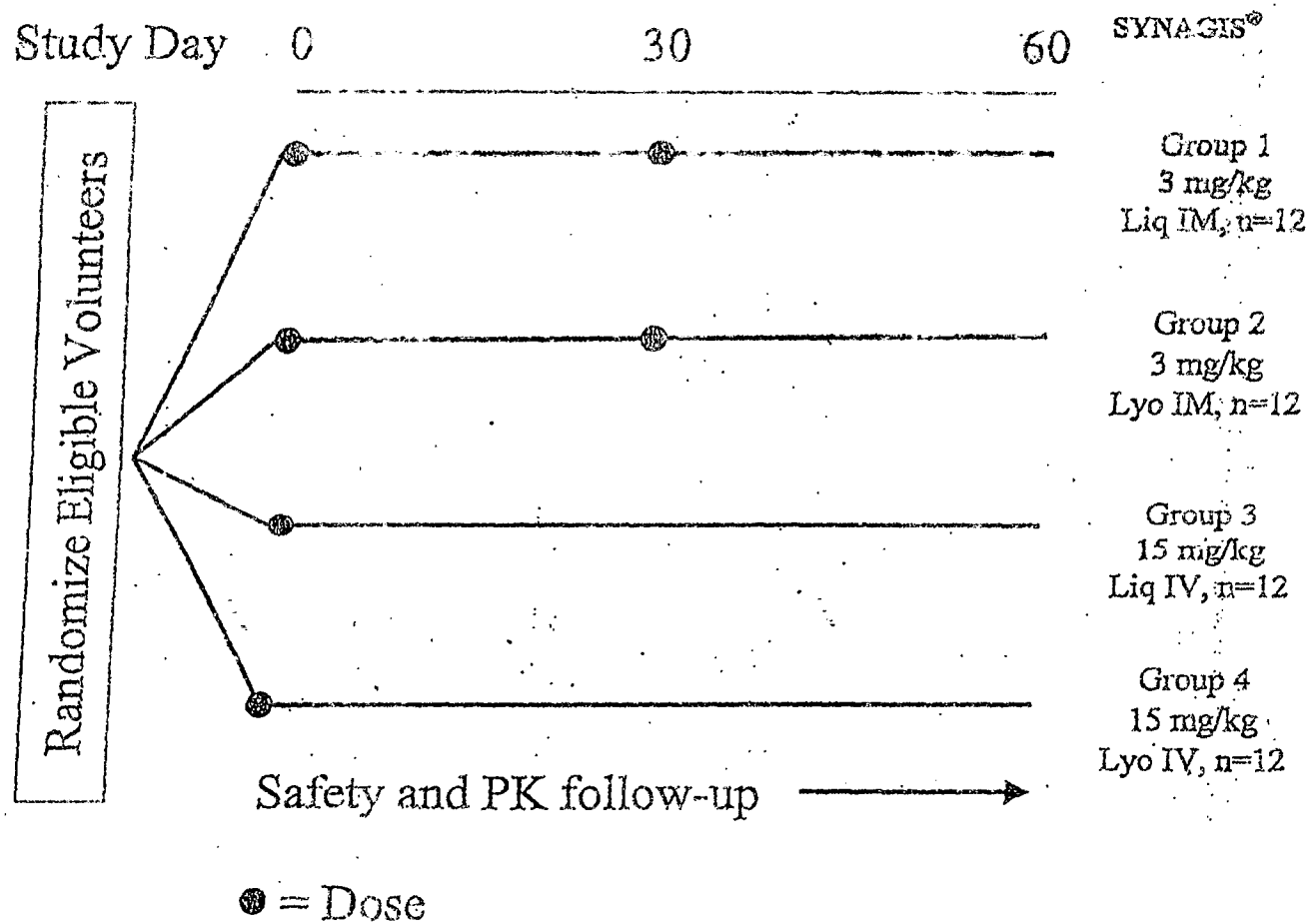


Fig. 2

695 98

SEQUENCE LISTING

<110> MedImmune, Inc.
<120> STABILIZED LIQUID ANTI-RSV ANTIBODY FORMULATIONS
<130> 10271-026-228
<140>
<141>
<150> 50/388,921
<151> 2002-06-14
<160> 6
<170> PatentIn version 3.1
<210> 1
<211> 7
<212> PRT
<213> Homo sapiens
<400> 1
Thr Ser Gly Met Ser Val Gly
1 5
<210> 2
<211> 16
<212> PRT
<213> Homo sapiens
<400> 2
Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15
<210> 3
<211> 10
<212> PRT
<213> Homo sapiens
<400> 3
Ser Met Ile Thr Asn Trp Tyr Phe Asp Val
1 5 10
<210> 4
<211> 10
<212> PRT
<213> Homo sapiens
<400> 4
Lys Cys Gln Leu Ser Val Gly Tyr Met His
1 5 10
<210> 5
<211> 7
<212> PRT
<213> Homo sapiens

696 *Q7*

WO 03/105894

PCT/US03/18913

<400> 5

Asp Thr Ser Lys Leu Ala Ser

1 5

<210> 6

<211> 9

<212> PRT

<213> Homo sapiens

<400> 6

Phe Gln Gly Ser Gly Tyr Pro Phe Thr

1 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18913

A. CLASSIFICATION OF SUBJECT MATTER

PC(7) : A61K 39/385, 39/42; C07K 16/00
 US CL : 424/130.1, 141.1, 147.1; 530/387.1, 388.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 141.1, 147.1; 530/387.1, 388.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/55217 A1 (MEDIMMUNE, INC.) 02 August 2001 (02.08.2001), see entire document.	1-39
Y	WO 01/64751 A2 (MEDIMMUNE, INC.) 07 September 2001 (07.09.2001), see entire document.	1-39

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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

Date of the actual completion of the international search

26 October 2003 (20.10.2003)

Date of mailing of the international search report

03 NOV 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

JENNIFER GRASER

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18913

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 40-45
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

700 100
✓

INTERNATIONAL SEARCH REPORT

PCT/US03/19913

OK
100
Folios
(sin poder)

Continuation of B. FIELDS SEARCHED Item 3:

DIALOG, WEST, MEDLINE

search terms: synagis, rsv, respiratory syncytial virus, SEQ ID NOs: 1-6

701 tot

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-038013- -00004-0000

Fecha: 2009-03-30 14:14:50 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 100

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 038.013
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN DE ANTICUERPO EN
AMORTIGUADOR DE ACETATO DE HISTIDINA"
Solicitante : GENENTECH, INC
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 599 del 31 de Diciembre de 2008

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de agente oficioso de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**FORMULACIÓN DE ANTICUERPO EN AMORTIGUADOR DE ACETATO DE HISTIDINA**", cuyo titular es **GENENTECH, INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular ACETATO DE HISTIDINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 17 de abril de 2007 reivindicando prioridad bajo la solicitud US20040620413P del 2004-10-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 599 del 31 de Diciembre de 2008, cuya publicación internacional corresponde a la WO2006044908 del 2006-04-27.
- 2.2. La solicitud colombiana 07 038.013 objeto de la presente oposición, se refiere a una formulación farmacéutica estable que comprende un anticuerpo monoclonal en un amortiguador de acetato de histidina, pH 5.5 a 6.5; en donde el pH es desde 5.8 a 6.2; en donde la concentración del amortiguador de acetato de histidina es desde alrededor de 1mM a alrededor de 200mM; en donde la concentración del amortiguador de acetato de histidina es desde alrededor de 10mM a alrededor de

40mM; en donde la concentración de anticuerpo es desde alrededor de 10mg/mL a alrededor de 250mg/mL; en donde la concentración del anticuerpo monoclonal es desde alrededor de 20mg/mL a alrededor de 40mg/mL; en donde la concentración del anticuerpo monoclonal es desde alrededor de 80mg/mL a alrededor de 250mg/mL; y, que comprende además un sacárido; en donde el sacárido es un disacárido.

2.3. En primera instancia, se debe advertir que algunas reivindicaciones se refieren al método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación de la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14: "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20: "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al método de tratamiento no sería patentable.

2.4. Anora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- o D1: WO03105894 publicada el 24 de diciembre de 2003.

2.5. Ahora bien, el documento D1, particularmente en la descripción define una formulación líquida estabilizada de anticuerpos Anti-RSV. Particularmente, esta anterioridad D1 revela formulaciones líquidas de antígenos las cuales exponen estabilidad, bajo los niveles imperceptibles de fragmentación del anticuerpo, bajo los niveles imperceptibles de agregación, y muy poco a ninguna pérdida de actividad biológica, aún durante o después de periodos largos de almacenaje. Según dicha anterioridad D1 en la página 21, líneas 2 y 3, se define una formulación farmacéutica estable que comprende un anticuerpo con un pH de 5.0 a 7.0, preferiblemente 5.5 en un búfer de histidina. Según esta anterioridad, la sal de histidina usada puede ser de acetato, tal y como lo evidencia en la página 20 línea 30, de dicho documento D1. Por lo tanto además que la presente solicitud comprende un método terapéutico no patentable a luz de la norma colombiana, también revela una formulación líquida de antígenos con el mismo pH en un amortiguador de acetato de histidina que no es novedoso como lo indica esta solicitud anterior D1 de 2003 que revela con anterioridad tal formulación. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 038.013 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 20 de octubre de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una formulación líquida de antígenos con el mismo pH en un amortiguador de acetato de histidina, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la*

tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMULACIÓN DE ANTICUERPO EN AMORTIGUADOR DE ACETATO DE HISTIDINA"**, cuyo titular es **GENENTECH, INC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 599 del 31 de diciembre de 2008.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03105894 publicada el 24 de diciembre de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

• D1: WO03105894 publicada el 24 de diciembre de 2003

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.