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Act. 444 RESPUESTAREQUE Folios: 19

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

00001

Referencia: Expediente No. 07.039.669

Solicitud de Patente de Invención titulada: "Uso de un inhibidor Mtor en el
tratamiento de leiomioma uterino"

Solicitante: Wyeth

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 297**DEL 17 DE AGOSTO DE 2007, OFICIO NO. 9881 (EXAMEN DE FORMA)**

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

1. Presento copia debidamente legalizada del documento en que consta la cesión del derecho a la patente del inventor a la entidad solicitante.
2. Aprovecho esta oportunidad para presentar una copia del Reporte Preliminar Internacional sobre Patentabilidad que fue emitido por la Autoridad de Búsqueda del PCT.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexos: Documento de Cesión de Inventores

Reporte Preliminar Internacional sobre Patentabilidad

BOGATM/BOGDMS-87285.DOC

APOSTILLA

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1. País: Estados Unidos de América
Este documento público
2. Ha sido firmado por MELODY L. MARSDEN
3. Quien actúa en calidad de NOTARIO PÚBLICO
4. Lleva el sello de MELODY L. MARSDEN, NOTARIO PÚBLICO,
CONDADO DE FILADELFIA, ESTADO DE PENNSILVANIA

Certificado

5. En Harrisburg, Pensilvania
6. El 02 de mayo de 2007
7. Por Pedro A. Cortés, Secretario del Estado de Pensilvania
8. N°: 200717025
9. Sello (Aparece adherido sello dorado de la Secretaría de Estado de Pensilvania)
10. Firma (firmado) Pedro A. Cortés


JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Estado de Pensilvania

Condado de Montgomery

El 29 de marzo de 2007, certifico que el documento anterior/anexo es una fotocopia verdadera, exacta, completa e inalterada hecha por Sandra Weiss de un documento de Cesión suscrito por el mencionado cedente Robert R. Ruffolo, Jr. el 11 de enero de 2004.

[Firmado] Melody L. Marsden, Notario Público

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TRADUCCIÓN OFICIAL N° 110507 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

[Sello en tinta que dice: "Sello notarial. Melody L. Marsden, Notario Público. Lower Gwyned Twp., Condado de Montgomery. Mi comisión vence el 26 de julio de 2008"]

[Sello realzado que dice: "Melody L. Marsden, Notario Público. Estado de Pensilvania"]

[En la esquina superior derecha de cada página de la Cesión de Invención aparece lo siguiente: "Archivo N°: AM-101846L1 Patentes"]

[En la parte inferior de cada página de la Cesión de Invención aparece lo siguiente: "Cesión de Invención Solicitud Provisional"]

Cesión de Invención

En consideración del pago por la CESIONARIA a la CEDENTE de una contraprestación válida y suficiente cuyo recibo se acusa por medio del presente, los CEDENTES:

- (1) Nombre Completo del Inventor: Robert R. Ruffolo, Jr.
Residencia: 725 Pughtown Road, Spring City, PA 19475
Ciudadanía: Estados Unidos de América

por medio del presente vende, cede y transfiere a la CESIONARIA, **JAIME A. GARAVITO B**

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

y los sucesores, CESIONARIOS y representantes legales de la CESIONARIA, la totalidad del derecho, título e intereses para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todos los derechos a reivindicar prioridad con respecto a la invención titulada:

MÉTODO DE TRATAMIENTO DEL LEIOMIOMA UTERINO

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e inventada por los CEDENTES y los siguientes inventores adicionales, si los
hubiere:

y que se encuentra en la Solicitud Provisional de los EE.UU. No. 60/622.917
presentada el 28 de octubre de 2004

[También verifique si se están cediendo solicitud(es) adicional(es)]

X y cualquier equivalente legal de las mismas en un país extranjero

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la fecha de presentación y el número de solicitud de dicha solicitud de los EE.UU.
cuando se conozca, se debe insertar arriba, incluyendo el derecho a invocar
prioridad, incluyendo todas y cada una de las mejoras divulgadas en la misma y
en todas las patentes obtenidas para dicha invención a través de la anterior
solicitud y cualquier solicitud provisional, no provisional, continuación, divisional,
renovación o sustitución de la misma presentada posteriormente y en cuanto a la
patente, cualquier re-expedición o nuevo examen de la misma.

Jaime Garavito
JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

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Los CEDENTES por medio del presente acuerdan que no se ha hecho ni se
hará o suscribirá ninguna cesión, venta, acuerdo o gravamen que pueda estar
en conflicto con esta cesión.

Los CEDENTES autorizan a la CESIONARIA para que haga solicitudes y para
que reciban patentes para dicha invención en cualquiera de los mencionados
países en su propio nombre, o en el nombre de la CEDENTE o a su elección.

Los CEDENTES acuerdan suscribir u obtener cualquier seguridad adicional
necesaria del título a dicha invención y cualquier patente que pueda ser
expedida para la misma y a entregar en cualquier momento y a solicitud y

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expensas de la CESIONARIA cualquier testimonio en cualquier derecho preexistente que impida el patentamiento de la invención, litigio o procedimiento relacionado y a suscribir todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título a dicho invento o cualquier patente que pueda ser otorgada para el mismo a la CESIONARIA, sus sucesores, CESIONARIOS u otros representantes legales y a suscribir, en cualquier momento, a solicitud y expensas de la CESIONARIA, cualquier continuación, continuación parcial, divisional, renovación o sustitución de la misma y en cuanto a patentes a re-expedir o re-examinar las mismas, o cualesquier otras solicitudes adicionales de patentes para dicho invento o cualquier parte del mismo, todas las cuales y cualquier patente que se expida se ceden por medio del presente a la CESIONARIA y prestará todos los juramentos legales o declaraciones y hará todos los actos legales requeridos para adquirirlos, sin compensación adicional, pero a expensas de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

Los CEDENTES autorizan y solicitan al Comisionado de Patentes expedir todas y cada una de las patentes de los Estados Unidos para dicho invento, que resulte de cualquiera de las solicitudes a su CESIONARIA.

(Firmado)
Robert R. Ruffolo, Jr.

Octubre 11, 2004
Fecha

RECONOCIMIENTO

Estado de Pensilvania)
Condado de Montgomery)

Declaración juramentada

Jaime A. Garavito B.
JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

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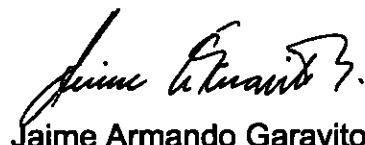
TRADUCCIÓN OFICIAL N° 110507 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

El 11 de noviembre de 2004, Robert R. Ruffolo, Jr., compareció personalmente ante mí, a quien conozco como la persona describa en el anterior instrumento y quien suscribió el mismo y reconoció haberlo suscrito en forma libre y espontánea para los fines consignados en él.

(Firmado) Bubinea Owens, Notario Público

[Sello en tinta que dice: "Bubinea Owens, Notario Público. Upper Providence Twp., Condado de Montgomery. Mi comisión vence el 07 de abril de 2007"]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.



Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 77888



APOSTILLE

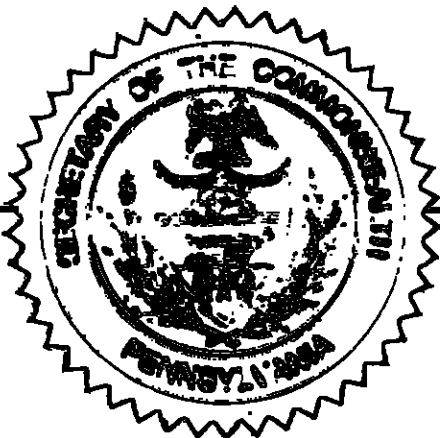
(Convention de La Haye du 5 octobre 1961)

1. Country : United States Of America
2. This public document has been signed by **MELODY L MARSDEN**
3. acting in the capacity of **NOTARY PUBLIC**
4. bears the seal/stamp **MELODY L MARSDEN, NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OF PENNSYLVANIA**
5. at Harrisburg, Pennsylvania
6. The 2nd day of May, 2007
7. by Pedro A. Cortés, Secretary of the Commonwealth of Pennsylvania
8. No : 200717025
9. Seal/Stamp
10. Signature

Certified

Pedro A. Cortés

Pedro A. Cortés

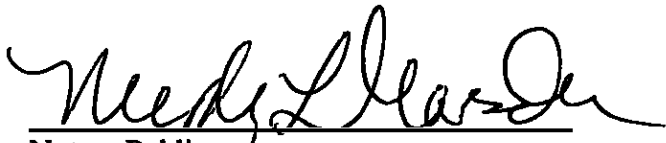


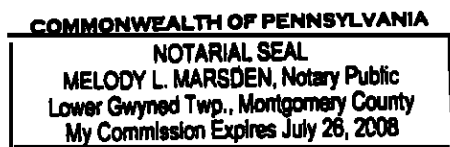
notary 97

State of Pennsylvania

County of Montgomery

On March 29, 2007, I certify that the preceding/attached document is a true,
exact, complete and unaltered photocopy made by Sandra Weiss of an Assignment document
executed by the named Assignor Robert R. Ruffolo, Jr. on January 11, 2004.


Notary Public



92

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Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

- (1) Full Name of Inventor: Robert R. Ruffolo, Jr.
Residence: 725 Pughtown Road, Spring City, PA 19475
Citizenship: US

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:

METHOD OF TREATING UTERINE LEIOMYOMA

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/622,917 filed on: October 28, 2004

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country,

the date of filing and application number of said U.S. application when known, to be inserted above, including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

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Date _____

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From the INTERNATIONAL BUREAU

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PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)
(PCT Rule 44bis.1(c))

To:

KODROFF, Cathy, A.
Howson and Howson
321 Norristown Road, Suite 200
Spring House Corporate Center, P.O. Box 457
Spring House, Pennsylvania 19477
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 10 May 2007 (10.05.2007)		
Applicant's or agent's file reference AM-101846PCT	IMPORTANT NOTICE	
International application No. PCT/US2005/039836	International filing date (day/month/year) 21 October 2005 (21.10.2005)	Priority date (day/month/year) 28 October 2004 (28.10.2004)
Applicant WYETH et al		

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

MAY 21 2007

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nora Lindner
Facsimile No. +41 22 338 82 70	e-mail: pt02.pct@wipo.int

Applicant's or agent's file reference AM-101846PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2005/039836	International filing date (day/month/year) 21 October 2005 (21.10.2005)	Priority date (day/month/year) 28 October 2004 (28.10.2004)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant WYETH			

1.

This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2.

This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3.

This report contains indications relating to the following items:

☒

Box No. I

Basis of the report

☒

Box No. II

Priority

☐

Box No. III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

☐

Box No. IV

Lack of unity of invention

☒

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

☐

Box No. VI

Certain documents cited

☐

Box No. VII

Certain defects in the international application

☐

Box No. VIII

Certain observations on the international application

4.

The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 01 May 2007 (01.05.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt02.pct@wipo.int

PATENT COOPERATION TREATY

96

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 24 FEB 2006

PCT PCT

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To:

see form PCT/ISA/220

4/5

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2005/039836International filing date (day/month/year)
21.10.2005Priority date (day/month/year)
28.10.2004International Patent Classification (IPC) or both national classification and IPC
A61K31/00, A61K31/436, A61K31/445, A61P15/00, A61P35/00Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Paul Soto, R

Telephone No. +49 89 2399-7346



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/039836

97

11/11/15

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/039836

98

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-7
	No: Claims	8-23
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-23
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US 2004/106637 A1 (GUAN KUN-LIANG) 3 June 2004

D2: WALKER CHERYL LYN ET AL: "Uterine leiomyoma in the Eker rat: A unique model for important diseases of women." GENES CHROMOSOMES & CANCER, vol. 38, no. 4 (2003-12), pages 349-356, XP009062056 ISSN: 1045-2257

D3: US 2003/144204 A1 (SPENCER DAVID) 31 July 2003

D4: WO 99/01118 A (ATHEROGENICS, INC; CHINERY, REBECCA; BEAUCHAMP, R., DANIEL; COFFEY, RO) 14 January 1999

2. The present application relates to *the use* of an mTOR inhibitor (**claim 1**), of a rapamycin (**claim 2**) and of the rapamycin 42-ester CCI-779 (**claim 7**) *in the preparation of a medicament useful in the treatment or inhibition of uterine leiomyoma in a mammal*.

The present application further relates to a *pharmaceutical composition* useful in treating or inhibiting uterine leiomyoma in a mammal comprising an mTOR inhibitor (**claim 8**), or a rapamycin (**claim 9**) or the compound CCI-779 (**claim 14**) in unit dosage form in association with a pharmaceutically acceptable carrier; and to a *pharmaceutical pack* containing a course or treatment of uterine leiomyoma for one individual mammal, said pack comprising a container having a unit of an mTOR inhibitor (**claim 15**), a rapamycin (**claim 17**) or the compound CCI-779 (**claim 22**) in unit dosage form.

3.1. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

mTOR inhibitors in general but also rapamycins and in particular rapamycin (Sirolimus), 42-O-(2-hydroxy)ethyl rapamycin (Certican, Everolimus) and the 42-ester CCI-779 (Temsirolimus) are well known in the pharmaceutical field and have been extensively used as antifungal, antineoplastic, macrolide, and immunosuppressive agents, whereby

neither the pharmaceutical compositions according to present claims 8-14 nor the pharmaceutical packs according to present claims 17-23 are novel. It should be noted that the technical features referring to the medical indication intended for the compositions or the packs, namely the treatment of uterine leiomyoma in a mammal, do not limit in any way the scope of present claims 8-23 because a pharmaceutical composition or pack is defined by its active pharmaceutical components and not by the medical indication intended for it.

- 3.2. Present claims 1-7 are novel over the prior art. In particular **D1** discloses methods to treat disorders which are caused by mutations in the TSC1 or TSC2 genes, such as tuberous sclerosis, the methods comprising the administration of S6K or mTOR inhibitors, such as rapamycin or rapamycin derivatives. However, the document does not explicitly mention the treatment of uterine leiomyoma, whereby it is not novelty destroying for present claims 1-7.

- 4.1. No inventive step (Art. 33(3) PCT) is recognised for that subject-matter which is not novel, namely for claims 8-23.

- 4.2. The subject-matter of present claims 1-7 does also not involve an inventive step for the following reasons.

D1, which is regarded as the closest prior art, discloses the use of S6K or mTOR inhibitors, and in particular rapamycin and derivatives thereof, for the treatment of disorders which are caused by mutations in the TSC1 or TSC2 genes. The present application differs from **D1** in that mTOR inhibitors are used specifically for the treatment of uterine leiomyoma.

Thus, the *problem* to be solved by the present application is regarded in the provision of further medical utilities for rapamycins and other mTOR inhibitors. The *solution* provided by the present application is rendered obvious by **D2**. This document (see the abstract) discloses that Eker rats carry a defect in the TSC-2 tumour suppressor gene and that female Eker rats develop uterine leiomyoma with a high frequency (see also page 14, lines 1-11 of the application). Thus, the skilled person would consider uterine

- 5.2. For the assessment of the present **claims 1-7** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment, as it is the case of present claims 1-7.