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Herrera
a Ravid
: Porras

Medellín
Múnera
driguez

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S.

Re.: Expediente No. 09-041.795
Solicitud de Patente de Invención titulada: "COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN NILOTINIB O SU SAL"
Solicitante: NOVARTIS AG
Nuestra Ref.: P2009/000035

MEMORIAL DE ALCANCE

CARLOS R. OLARTE, 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, me permito dar alcance al memorial de respuesta al examen de fondo radicado hoy 21 de agosto de 2013, para adjuntar el anexo 1 citado en el mismo ya que por un error involuntario se omitió.

Atentamente,

CARLOS R. OLARTE
CC. No.79.782.747 de Bogotá
T.P. 74.295

Adjunto: Anexo 1 Declaración Juramentada del Dr. Tsu-Han Lin presentada durante el trámite de la solicitud de patente en Estados Unidos.

Appendix I

CASE PAT034385-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Manley, Paul W. et al.

Art Unit: 1624
Examiner: Balasubramanian, V
Conf. No.:

INTERNATIONAL APPLICATION NO: PCT/US2006/027878

FILED: July 18, 2006

U.S. APPLICATION NO: 11/995898

35 USC §371 DATE: January 16, 2008

FOR: Salts of 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, Tsu-Han Lin, declare as follows:

1. I received a Ph.D. in Pharmaceutical Science from University of Tokyo, Japan in 1986.

2. I have worked at Novartis Pharmaceuticals Corporation in the area of Drug Metabolism & Pharmacokinetics (DMPK) / Absorption, Distribution, Metabolism and Excretion (ADME) Section since 2001.

3. Prior to working at Novartis Pharmaceuticals Corporation, I worked in this field at Merck for three years and then Southern Research Institute for 11 years.

4. Based on my education and experience, I consider myself to be an expert in DMPK, especially the ADME area.

5. The following is a summary of the results obtained from experiments that were conducted by me or under my supervision relating to the relative bioavailability in dogs of the free base and monohydrochloride salt of AMN107 (also known as nilotinib):

Animal species/strain/gender	Dog/Beagle/male	
Animal number	3	
Route	Oral gavage	
Formulation	AMN107 free base Suspension in 0.5% HPMC aqueous solution with 0.05% Tween 80	AMN107•HCl monohydrate Suspension in 0.5% HPMC aqueous solution with 0.05% Tween 80
Dose (mg/kg, free base equivalent)	20	18
Samples collected	Serial blood at designated timepoints up to 48 h postdose	
Samples analyzed	Serial plasma samples were analyzed for the parent by LC/MS/MS	
C_{max} (ng/mL)	132 ± 72	1530 ± 410
t_{max} (h)	2.0 ± 0.0	1.3 ± 0.6
AUC_{0-48h}(ng•h/mL)	790 ± 247	9300 ± 2780
$AUC_{0-\infty}$ (ng•h/mL)	897 ± -[a]	9270 ± 2800
Relative bioavailability (%)[b]	7.6	100

[a] Only two dogs since one of three dogs had an unreliable terminal slope

[b] HCl salt value was normalized to 100%

The dog bioavailability of AMN107 as free base or HCl salt was tested at the dose of 20 mg/kg in the dog. The test articles were prepared as suspension form in 0.5% HPMC aqueous solution containing 0.05% Tween 80. The relative bioavailability (%) of the AMN107 free base to the HCl salt form (normalized to 100%) was calculated based on the plasma AMN107 data according to the following equation assuming a proportional relationship between AUC0-48h and dose:

$$Relative\ bioavailability\ (\%) = \frac{AUC_{0-48h,\ free\ base} \times Dose_{HCl\ salt}}{AUC_{0-48h,\ HCl\ salt} \times Dose_{free\ base}}$$

An absorption prediction was performed using GastroPlus™ (ver. 3.2.05, Simulations Plus, Lancaster, CA) using the data of the Caco-2 permeability (7.1×10^{-5} cm/min) and physicochemical properties (solubility 0.002 mg/mL at pH6.8 for the free base and 0.14 mg/mL in water for HCl salt). The bioavailability for the HCl salt was approximately 13-fold higher than the free base as indicated by its relative bioavailability calculated from their AUC values. The GastroPlus predicted absorption was in a good agreement with that for the relative bioavailability observed in the dog. However, the later studies with other salts demonstrated that the *in vivo* system is much more complicated and cannot be simply predicted based on only CaCo-2 permeability and the compound solubility.

6. The 13-fold higher oral bioavailability of the hydrochloride salt is an advantage which permits patients to take less drug to achieve comparable plasma levels and could not have been reliably predicted.

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

Tsu-Han Lin Ph.D.

Date: 06-Feb-2012

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Expediente No. 09-041.795 Memorial de alcance a respuesta examen de fondo

OlarteMoure Office <office@olartemoure.com> 21 de agosto de 2013 17:22
Para: info@sic.gov.co
Cc: Luz Marina Bulla <luz.bulla@olartemoure.com>, Francia Garcia <francia.garcia@olartemoure.com>
Cco: OlarteMoure Archivo <archivo@olartemoure.com>

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Estimados señores:

Por favor encuentren adjunto, un memorial de alcance a la respuesta al examen de fondo de la solicitud en referencia radicada hoy 21 de agosto de 2013. (Adjunto copia para su referencia).

Rogamos acusar recibo.

Atentamente,

Office
OLARTEMOURE
Carrera 5 N° 34-03
Bogotá, Colombia 110311
Tel : +57 1 601-7700
Fax : +57 1 601-7799
office@olartemoure.com
www.olartemoure.com

2 archivos adjuntos

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