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(30) Priority: **27.03.2013 US 201361805860 P**  
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(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:  
**14774938.6 / 2 979 087**

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(54) **USE OF BIOMARKERS FOR ASSESSING TREATMENT OF GASTROINTESTINAL INFLAMMATORY DISORDERS WITH BETA7 INTEGRIN ANTAGONISTS**

(57) Methods of assessing or monitoring the effect, efficacy, responsiveness to treatment, and/or determining a dose or dosing regimen of therapeutic agents, such as integrin beta7 antagonists, for the treatment of gastrointestinal inflammatory disorders are provided. In certain aspects, methods of using integrin beta7 subunit-containing receptor occupancy by the integrin beta7 antagonist on colonic lymphocytes as an indicator ("biomarker") of the effect, efficacy, or responsiveness to treatment, and/or as a means to determine dosing or dos-

ing regimens of therapeutic agents such as beta7 integrin antagonists for the treatment of gastrointestinal inflammatory disorders are provided. In certain aspects, methods of assessing the effect, efficacy, or responsiveness to beta7 integrin antagonist treatment by measuring gene expression levels of one or more integrin receptor ligands, lymphocyte genes, cytokine genes, or the number of alphaE-positive cells in intestinal crypt epithelium are provided.

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EUROPEAN SEARCH REPORT

Application Number  
EP 18 19 1598

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	SOLER DULCE ET AL: "The Binding Specificity and Selective Antagonism of Vedolizumab, an Anti-alpha(4)beta(7) Integrin Therapeutic Antibody in Development for Inflammatory Bowel Diseases", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, vol. 330, no. 3, 1 September 2009 (2009-09-01), pages 864-875, XP009134512, ISSN: 0022-3565, DOI: 10.1124/JPET.109.153973 [retrieved on 2009-06-09]	1-4, 12-15, 20,21, 23-37	
Y	* pages 866,870; figures 4,6,7 *	5-11, 16-19,22	
X	WO 2009/140684 A2 (GENENTECH INC [US]; GELZLEICHTER THOMAS RICHARD [US] ET AL.) 19 November 2009 (2009-11-19) * claims 1-4; examples 1,2 *	1-11, 23-37	
Y	DULCE SOLER-FERRAN ET AL: "Integrin [alpha]4[beta]7 Antagonists: Activities, Mechanisms of Action and Therapeutic Prospects", CURRENT IMMUNOLOGY REVIEWS, vol. 8, no. 2, 1 March 2012 (2012-03-01), pages 118-134, XP055237573, NL ISSN: 1573-3955, DOI: 10.2174/157339512800099666 * the whole document *	1-37	TECHNICAL FIELDS SEARCHED (IPC)
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The present search report has been drawn up for all claims			
Place of search <b>Munich</b>		Date of completion of the search <b>11 June 2019</b>	Examiner <b>Pinheiro Vieira, E</b>
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

3 EPO FORM 1503 03.82 (P04C01)



EUROPEAN SEARCH REPORT

Application Number  
EP 18 19 1598

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	VERMEIRE S ET AL: "The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study", GUT, BRITISH MEDICAL ASSOCIATION, LONDON, UK, vol. 60, no. 8, 1 January 2011 (2011-01-01), pages 1068-1075, XP009189327, ISSN: 0017-5749, DOI: 10.1136/GUT.2010.226548 * figures 1,4; table 3 *	1-37	
E	WO 2014/055824 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]) 10 April 2014 (2014-04-10) * claims 1-28; figures 7-11,13 *	1-37	
X,D	WO 2012/135589 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH] ET AL.) 4 October 2012 (2012-10-04) * Pages 67-71, 85, 86; figure 5; examples 1,2 *	1-11, 23-37	
Y		12-22	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (IPC)
Place of search Munich		Date of completion of the search 11 June 2019	Examiner Pinheiro Vieira, E
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

3 EPO FORM 1503 03.02 (P04C01)



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**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing claims for which payment was due.

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Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

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No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

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**LACK OF UNITY OF INVENTION**

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

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see sheet B

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All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

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As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

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Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

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None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

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The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

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**LACK OF UNITY OF INVENTION  
SHEET B**

Application Number  
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

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1. claims: 5-11(completely); 1-4, 23-37(partially)

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A method of determining or monitoring the efficacy of an integrin beta7 antagonist for treatment of a gastrointestinal inflammatory disorder in a patient or in an antagonist treated patient in a placebo-controlled clinical trial; or the responsiveness of a patient having gastrointestinal inflammatory disorder to treatment with an integrin beta7 antagonist. The method comprises determining a biomarker in a sample and wherein the biomarker is integrin beta7 subunit-containing receptor occupancy by the antagonist on colonic lymphocytes.

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2. claims: 12-15(completely); 1-4, 20, 21, 23-37(partially)

A method of determining or monitoring the efficacy of an integrin beta7 antagonist for treatment of a gastrointestinal inflammatory disorder in a patient or in an antagonist treated patient in a placebo-controlled clinical trial; or the responsiveness of a patient having gastrointestinal inflammatory disorder to treatment with an integrin beta7 antagonist. The method comprises determining a biomarker in a sample and wherein the biomarker is gene expression levels of one or more integrin receptor ligands.

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3. claims: 16, 17(completely); 1-4, 20, 21, 23-37(partially)

A method of determining or monitoring the efficacy of an integrin beta7 antagonist for treatment of a gastrointestinal inflammatory disorder in a patient or in an antagonist treated patient in a placebo-controlled clinical trial; or the responsiveness of a patient having gastrointestinal inflammatory disorder to treatment with an integrin beta7 antagonist. The method comprises determining a biomarker in a sample and wherein the biomarker is gene expression levels of one or more lymphocyte genes

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4. claims: 18, 19(completely); 1-4, 20, 21, 23-37(partially)

A method of determining or monitoring the efficacy of an integrin beta7 antagonist for treatment of a gastrointestinal inflammatory disorder in a patient or in an antagonist treated patient in a placebo-controlled clinical trial; or the responsiveness of a patient having gastrointestinal inflammatory disorder to treatment with an integrin beta7 antagonist. The method comprises determining a biomarker in a sample and wherein the biomarker is gene expression levels of one or more cytokines.

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**LACK OF UNITY OF INVENTION  
SHEET B**Application Number  
EP 18 19 1598

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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

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5. claims: 22(completely); 1-4, 23-37(partially)

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A method of determining or monitoring the efficacy of an integrin beta7 antagonist for treatment of a gastrointestinal inflammatory disorder in a patient or in an antagonist treated patient in a placebo-controlled clinical trial; or the responsiveness of a patient having gastrointestinal inflammatory disorder to treatment with an integrin beta7 antagonist. The method comprises determining a biomarker in a sample and wherein the biomarker is the number of alphaE-positive cells in intestinal crypt epithelium.

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ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.

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5 This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

11-06-2019

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	使用生物标志物评估用β7整联蛋白拮抗剂治疗胃肠炎性疾病		
公开(公告)号	<a href="#">EP3495814A3</a>	公开(公告)日	2019-07-17
申请号	EP2018191598	申请日	2014-03-26
申请(专利权)人(译)	F.霍夫曼罗氏公司		
当前申请(专利权)人(译)	F.霍夫曼罗氏公司		
[标]发明人	DIEHL LAURI KEIR MARY TANG MEINA TAO WEI XIAOHUI WILLIAMS MARNA B		
发明人	DIEHL, LAURI KEIR, MARY TANG, MEINA TAO WEI, XIAOHUI WILLIAMS, MARNA B.		
IPC分类号	G01N33/00 G01N33/53		
CPC分类号	C07K16/2839 C12Q1/6883 C12Q2600/106 C12Q2600/158 G01N33/6893 G01N2333/70546 G01N2800/065 G01N2800/52 G01N33/53		
优先权	61/805860 2013-03-27 US 61/914619 2013-12-11 US PCT/US2014/031825 2014-03-26 WO		
其他公开文献	EP3495814A2		
外部链接	<a href="#">Espacenet</a>		

摘要(译)

提供了评估或监测治疗剂的效果，功效，响应性和/或确定治疗剂（例如整联蛋白β7拮抗剂）的剂量或给药方案的方法，用于治疗胃肠炎性疾病。在某些方面，使用整联蛋白β7拮抗剂占结肠淋巴细胞的整联蛋白β7亚基受体占据的方法作为对治疗的效果，功效或响应性的指示物（“生物标志物”），和/或作为确定给药的手段本发明提供了用于治疗胃肠炎性疾病的治疗剂如β7整联蛋白拮抗剂的给药方案。在某些方面，通过测量一种或多种整联蛋白受体配体，淋巴细胞基因，细胞因子基因或肠隐窝上皮细胞中αE阳性细胞数的基因表达水平来评估对β7整联蛋白拮抗剂治疗的效果，功效或响应性的方法。提供。

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim	CLASSIFICATION OF THE RELEVANT DOCUMENT
X	RUTGEERTS PAUL J ET AL: "A randomised phase I study of etrolizumab (rhMAB beta 7) in moderate to severe ulcerative colitis", GUT, vol. 59, no. 8, 20 June 2012 (2012-06-20), pages 1122-1130, XP02762363, * Figures 1-4; Tables 1-2 *	1-11, 23-37	INV. G01N33/00 G01N33/53
V	EG STEFANICH ET AL: "A humanized monoclonal antibody targeting the [beta]7 integrin selectively blocks intestinal homing of T lymphocytes", BRITISH JOURNAL OF PHARMACOLOGY, vol. 162, no. 8, 22 March 2013 (2013-03-22), pages 1855-1870, XP05515731, ISSN: 0954-1986, DOI: 10.1111/j.1476-5381.2011.01205.x * Figures 1-10 *	12-22 1-15, 20 21, 23-37	
V		16-19, 22	TECHNICAL FIELD (OR RELATED ARTS) C12Q G01N

The present search report has been drawn up for all claims

SEARCHED	SEARCHED	SEARCHED
INDEXED	INDEXED	INDEXED
CLASSIFIED	CLASSIFIED	CLASSIFIED
DATE OF SEARCH	DATE OF CLASSIFICATION OF THE REPORT	EXAMINER
Munich	11 June 2019	Pinheiro Vieira, E

CATEGORY OF CITED DOCUMENTS  
 X: particularly relevant to claim above  
 V: particularly relevant to remaining claims  
 Y: particularly relevant to remaining claims and/or dependent claims  
 A: technological background document  
 P: prior art document  
 F: information document  
 F: theory or principle underlying the invention  
 W: other literature  
 R: documents used for prior art search  
 A: member of the same patent family, corresponding document