

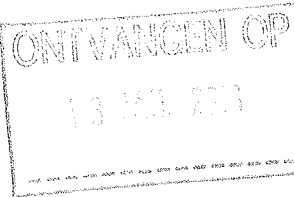
PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

Bar, Gregory Louis Joseph
GALAPAGOS NV
Generaal de Wittelaan L11 A3
B-2800 Mechelen
BELGIQUE



NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.2(c))

Date of mailing
(day/month/year) 11-01-16

Applicant's or agent's file reference
GAL-223-WO-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/EP2015/080430

International filing date (day/month/year)

18 December 2015 (18-12-2015)

Priority date (day/month/year)

22 December 2014 (22-12-2014)

Applicant

GALAPAGOS NV

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:



was transmitted to the International Bureau on see above date of mailing



has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:



because the necessary national security clearance has not yet been obtained



because (reason to be specified)

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Wilson, Patrick

PCT REQUEST

Print Out (Original in Electronic Form)

0	For receiving Office use only	
0-1	International Application No.	PCT/EP2015/080430
0-2	International Filing Date	18 DEC 2015 (18.12.2015)
0-3	Name of receiving Office and "PCT International Application"	RO/EP
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	CMS Online Filing Version CMS 1.11.2 MT/FOP 20020701/0.20.5.20
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	GAL-223-WO-PCT
I	Title of Invention	NOVEL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS AND OSTEOARTHRITIS
II	Applicant	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	GALAPAGOS NV
II-5	Address	Generaal De Wittelaan L11/A3 2800 Mechelen Belgium
II-6	State of nationality	BE
II-7	State of residence	BE
II-8	Telephone No.	+3215342900
II-9	Facsimile No.	+3215342901
II-10	e-mail	patents@glpg.com
II-10(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	as advance copies followed by paper notifications

PCT REQUEST

Print Out (Original in Electronic Form)

III-1	Applicant and/or inventor	
III-1-1	This person is	Applicant only
III-1-2	Applicant for	All designated States
III-1-4	Name	LES LABORATOIRES SERVIER
III-1-5	Address	35 rue de Verdun 92284 Suresnes France
III-1-6	State of nationality	FR
III-1-7	State of residence	FR
III-2	Applicant and/or inventor	
III-2-1	This person is	Inventor only
III-2-4	Name (LAST, First)	BREBION, Franck, Laurent
III-2-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-3	Applicant and/or inventor	
III-3-1	This person is	Inventor only
III-3-4	Name (LAST, First)	ALVEY, Luke, Jonathan
III-3-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-4	Applicant and/or inventor	
III-4-1	This person is	Inventor only
III-4-4	Name (LAST, First)	AMANTINI, David
III-4-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-5	Applicant and/or inventor	
III-5-1	This person is	Inventor only
III-5-4	Name (LAST, First)	DEPREZ, Pierre, Marc, Marie, Joseph
III-5-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-6	Applicant and/or inventor	
III-6-1	This person is	Inventor only
III-6-4	Name (LAST, First)	GOSMINI, Romain, Luc, Marie
III-6-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-7	Applicant and/or inventor	
III-7-1	This person is	Inventor only
III-7-4	Name (LAST, First)	JARY, Helène, Marie
III-7-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France

PCT REQUEST

Print Out (Original in Electronic Form)

III-8	Applicant and/or inventor	
III-8-1	This person is	Inventor only
III-8-4	Name (LAST, First)	PEIXOTO, Christophe
III-8-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-9	Applicant and/or inventor	
III-9-1	This person is	Inventor only
III-9-4	Name (LAST, First)	VARIN, Marie, Laurence, Claire
III-9-5	Address	Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville France
III-10	Applicant and/or inventor	
III-10-1	This person is	Inventor only
III-10-4	Name (LAST, First)	DE CEUNINCK, Frédéric, André
III-10-5	Address	75011 Paris France
III-11	Applicant and/or inventor	
III-11-1	This person is	Inventor only
III-11-4	Name (LAST, First)	POP-BOTEZ, Iuliana, Ecaterina
III-11-5	Address	53 Rue Anatole France 78800 Houilles France
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name (LAST, First)	BAR, Grégory, Louis, Joseph
IV-1-2	Address	Generaal De Wittelaan L11/A3 2800 Mechelen Belgium
IV-1-3	Telephone No.	+3215342980
IV-1-4	Facsimile No.	+3215342901
IV-1-5	e-mail	gregory.bar@glpg.com
IV-1-5(a))	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	as advance copies followed by paper notifications
IV-1-6	Agent's registration No.	9245590

PCT REQUEST

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V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	22 December 2014 (22.12.2014)
VI-1-2	Number	EP14307129.8
VI-1-3	Regional Office	EP
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VI-3	Incorporation by reference : where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	—
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	—
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	—
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	—
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	—

PCT REQUEST

Print Out (Original in Electronic Form)

RO/EP

IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	308	✓
IX-3	Claims	6	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	—
IX-6a	Sequence listing part of the description (also to be used for the purposes of international search)	—	✓
IX-7	TOTAL	320	

RO/EP

	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	—	✓
IX-18	PCT-SAFE physical media	—	—
IX-20	Figure of the drawings which should accompany the abstract		
IX-21	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	/Grégory Bar/	
X-1-1	Name (LAST, First)	BAR, Grégory, Louis, Joseph	
X-1-2	Name of signatory	Grégory Bar	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	(Agent)	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	18 DEC 2015 (18.12.2015)
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Bar, Gregory Louis Joseph
GALAPAGOS NV
Generaal de Wittelaan L11 A3
B-2800 Mechelen
BELGIQUE



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GAL-223-WO-PCT		Date of mailing (day/month/year) 19 February 2016 (19-02-2016)
International application No. PCT/EP2015/080430		International filing date (day/month/year) 18 December 2015 (18-12-2015)
Applicant GALAPAGOS NV		

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see PCT Applicant's Guide, International Phase, paragraphs 9.004 - 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer BENITEZ SIERRA, Olga Maria Tel: +49 (0)89 2399-5715
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GAL-223-WO-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2015/080430	International filing date (<i>day/month/year</i>) 18 December 2015 (18-12-2015)	(Earliest) Priority Date (<i>day/month/year</i>) 22 December 2014 (22-12-2014)
Applicant GALAPAGOS NV		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

5-[(PIPERAZIN-1-YL)-3-OXO-PROPYL]-IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS ADAMTS INHIBITORS FOR THE TREATMENT OF OSTEOARTHRITIS

5. With regard to the abstract,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

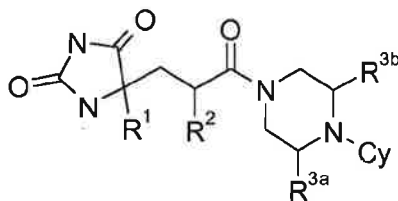
a. the figure of the **drawings** to be published with the abstract is Figure No. _____

- ☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention discloses compounds according to Formula I:



I

Wherein R, R², R^{3a}, R^{3b}, and Cy are as defined herein.

The present invention discloses compounds inhibiting ADAMTS, methods for their production, pharmaceutical compositions comprising the same and methods for the prophylaxis and/or treatment of inflammatory conditions and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/080430

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/06 A61K31/496 A61P19/02 A61P19/04
ADD.

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)

C07D

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/066151 A1 (LILLY CO ELI [US]) 1 May 2014 (2014-05-01) the whole document examples 1-5 page 24 - page 27; tables 1-4 claims 1-8 -----	1-18

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

29 January 2016

Date of mailing of the international search report

19/02/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Cortés, José

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/080430

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014066151 A1	01-05-2014	AU 2013334989 A1	23-04-2015
		CA 2886526 A1	01-05-2014
		CN 104755464 A	01-07-2015
		EA 201590621 A1	30-07-2015
		EP 2912021 A1	02-09-2015
		JP 2015535248 A	10-12-2015
		KR 20150058480 A	28-05-2015
		TW 201427955 A	16-07-2014
		US 2015218107 A1	06-08-2015
		WO 2014066151 A1	01-05-2014

Information on Search Strategy - Pilot phase (see OJ 2015, A86)

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

PCT/EP2015/080430

TITLE: 5-(PIPERAZIN-1-YL)-3-OXO-PROPYL-IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS ADAMTS INHIBITORS FOR THE TREATMENT OF OSTEOARTHRITIS

APPLICANT: GALAPAGOS NV

IPC CLASSIFICATION: C07D403/06, A61K31/496, A61P19/02, A61P19/04

EXAMINER: Cortés, José

CONSULTED DATABASES: WPI, CAPLUS

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: C07D403/06

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

Pharmacological activity: ADAMTS inhibitors

Medical use: inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis (osteoarthritis)

Chemical structure:

5-([4-(aryl/heteroaryl)-piperazin-1-yl]-3-oxo-propyl)-imidazolidine-2,4-dione derivatives

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2015/080430

International filing date (day/month/year)
18.12.2015

Priority date (day/month/year)
22.12.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/06 A61K31/496 A61P19/02 A61P19/04

Applicant
GALAPAGOS NV

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 and 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") except that 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 3 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.

Name and mailing address of the ISA:



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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Cortés, José

Telephone No. +49 89 2399-0



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.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-18</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in the present International Search Report:

D1 WO 2014/066151 A1 (LILLY CO ELI [US]) 1 May 2014 (2014-05-01)

Novelty (Article 33(2) PCT)

The present compounds differ from the compounds in D1 in the -CHR²-CO-piperidine (Ra)(Rb)Cy group.

The claimed matter is novel.

Inventive Step (Article 33(3) PCT)

D1 discloses N-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-ylmethyl)-3-(4-trifluoromethyl-phenyl)-propionamide derivatives as ADMTS-4/5 inhibitors for the treatment of osteoarthritis and cartilage erosion.

D1 is the closest prior art.

The problem of the invention was the provision of new ADAMTS inhibitors for the treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis (osteoarthritis).

The present description discloses exemplary compounds (e.g. pages 192 to 271, table III, compounds 001 to 481) covering essentially all structural variations of the present compounds as well as pharmacological data (e.g. pages 274 to 306, biological examples 3 and 4). It can therefore be assumed that the problem has been solved essentially over the whole of the claimed scope.

D1 discloses the structurally closest compounds of the same pharmacology and medical use.

The present compounds differ in many structural features from the compounds in D1. Nothing in D3 suggests the preparation of the present 5-[[4-(aryl/heteroaryl)-piperazin-1-yl]-3-oxo-propyl]-imidazolidine-2,4-dione derivatives.

D1 does not even disclose any piperazine derivatives.

The claimed matter is therefore not suggested by D1.

The claimed scope corresponds to the contribution to the prior art.

The claimed matter is based on an inventive step.

Re Item VII

Certain defects in the international application

Description

The description is not in line with the claim set.

Those parts of the pages 53 to 64 referring to "*clauses*" 1 to 126 are superfluous and misleading.

The relevant prior art D1 has not been cited in the description.

Some parts of the description refer to methods of medical treatment or medical uses as part of the claimed invention (e.g. [0001], [0020], [0021], [0026], [0033], [0084], [0172], [0173], [0176], [0179]).

Some parts of the description refer to structurally undefined "*prodrugs*" as part of the claimed invention (e.g. [0151]).

Some parts of the description refer to structurally undefined "*metabolites*" as part of the claimed invention (e.g. [0085], clause 1).

The description contains irrelevant expressions, like e.g.:

- "... *incorporated by reference* ..." (e.g. [0160], [0480])
- "*It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature, and intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. All such modifications coming within the scope of the appended claims are intended to be included therein. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.*" (e.g. [0479])

With entry into the regional phase before the EPO:

- The description has to be brought in line with the claim set.
- Those parts of the pages 53 to 64 referring to "*clauses*" 1 to 126 must be deleted.
- The relevant prior art D1 cited in the present search report must be cited in the description.

- Those parts of the application referring to methods of medical treatment or medical uses excluded from patentability as part of the claimed invention must be deleted or reformulated into an allowable form.
- Those parts of the application aimed at incorporating structurally undefined prodrugs or metabolites into the claimed scope must be deleted.
-
- Those parts of the application containing irrelevant or unnecessary expressions must be deleted.
- A working copy (e.g. hand-amended version) wherein the amendments are visible as well as a readable, re-typed version (clear copy) as the print version must be filed at the same time, in order to avoid printing errors (hand-amended pages are not allowed for the print version).
- The basis for the amendments in the application as originally filed must be indicated.

Re Item VIII

Certain observations on the international application

Lack of Clarity (Article 6 PCT)

The scope of claim 1 is unclear because of the functional feature "*biological active metabolites*" (page 311). This feature must be deleted in the claims and the respective parts of the description.

Those parts of the pages 53 to 64 referring to "*clauses*" 1 to 126 are superfluous and misleading and must be deleted.



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31 May 2017

By Email only

Galapagos NV

RE **GLPG ref** **GAL-223-CO-PCT**
 Your ref **please provide**
 Title **5-[(piperazin-1-yl)-3-oxo-propyl]-imidazolidine-2,4-dione**
 derivatives as ADAMTS inhibitors for the treatment of osteoarthritis

2800 Mechelen

Gen. De Wittekaan L11 A3

Dear Sirs,

Thanks for your email confirming that you are able to handle the national phase entry in Colombia of PCT Application PCT/EP2015/080430 for us.

Enclosed with this letter is the following information:

- PCT-RO-105 and "checklist" document; on these documents you can find priority, applicant and inventor info. Please pay attention that there are two applicants on this application, namely Galapagos NV and Les Laboratoires Servier.
- Word and pdf version of the patent specification in Spanish - *password will follow in subsequent email*
- Sequence listing in Spanish
- International Search Report and Written Opinion
- PCT inventors' assignment
- PCT declaration of entitlement under PCT rule 4.17(ii)

Fax: +32 15 342 901

Phone: +32 15 342 900

May we ask you to please download the full application as published (**WO2016/102347**) yourself from PatentScope.

We believe you now have everything needed to file this application in Colombia by the deadline of **22 July 2017** – please let us know however if anything further is needed.

Please also let us know as soon as possible by return email whether any other formality documents (Power of Attorney, Assignment or similar) would be needed to complete the filing procedure.

RPB Mechelen

BTW BE 0466.460.429

Kindly confirm safe receipt of these instructions.

Kind regards,



Julie Willems
Formalities Officer
IP Department
Galapagos NV

Encl:

- (1) PCT-RO-105
- (2) "checklist" document
- (3) Spanish patent specification – Word version
- (4) Spanish patent specification – PDF version
- (5) Sequence Listing
- (6) International Search Report and Written Opinion
- (7) PCT Assignment
- (8) PCT Declaration of entitlement under PCT rule 4.17