

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/US2018/027514	International filing date (day/month/year) 13.04.2018	Priority date (day/month/year) 13.04.2017
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International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K9/48 A61K47/10 A61K31/198 A61P35/00 A61P35/02

Applicant
ONCONOVA THERAPEUTICS, INC.

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 43*bis*.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 66.1*bis*(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 Peris Antoli, Berta Telephone No. +49 89 2399-0	
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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. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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	<u>1-32</u>
	No: Claims	<u>33-36</u>
Inventive step (IS)	Yes: Claims	<u>1-32</u>
	No: Claims	<u>33-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations

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

Reference is made to the following documents:

- D1 US 8 476 320 B2 (MANIAR MANOJ [US]; ET AL) 2 July 2013 (2013-07-02), cited in the application
- D2 US 8 063 109 B2 (BELL STANLEY C [US] ET AL) 22 November 2011 (2011-11-22), cited in the application
- D3 BOWLES D W et al.: "Phase I Study of Oral Rigosertib (ON 01910.Na), a Dual Inhibitor of the PI3K and Plk1 Pathways, in Adult Patients with Advanced Solid Malignancies", CLINICAL CANCER RESEARCH, vol. 20, no. 6, 3 February 2014 (2014-02-03), pages 1656-1665, XP055483800, cited in the application
- D4 OLNES M J et al.: "Directed therapy for patients with myelodysplastic syndromes (MDS) by suppression of cyclin D1 with ON 01910.Na", LEUKEMIA RESEARCH, NEW YORK, NY, US, vol. 36, no. 8, 21 April 2012 (2012-04-21), pages 982-989, XP028494957
- D5 US 2015/313859 A1 (MANIAR MANOJ [US] ET AL) 5 November 2015
- D6 DATABASE BIOSIS [Online], BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2013 (2013-11), RAZA AZRA ET AL: "Oral Rigosertib (ON 01910.Na) Treatment Produces A Encouraging Rate Of Transfusion Independence In Lower Risk Myelodysplastic Syndromes (MDS) Patients; A Genomic Methylation Profile Is Associated With Responses", XP002788716, Database accession no. PREV201400361728 ; & BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 2745, 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07-10, 2013
- D7 DATABASE BIOSIS [Online], BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2 December 2016 (2016-12-02), NAVADA SHYAMALA C ET AL: "Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS): Results from a Phase II Study", XP002788717, Database accession no. PREV201700341027 ; & BLOOD, vol. 128, no. 22, 2

December 2016 (2016-12-02), 58TH ANNUAL MEETING AND
EXPOSITION OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; SAN
DIEGO, CA, USA; DECEMBER 03 -06, 2016

- D8 DATABASE BIOSIS [Online], BIOSCIENCES INFORMATION SERVICE,
PHILADELPHIA, PA, US; December 2015 (2015-12), NAVADA
SHYAMALA C ET AL: "A Phase II Study of the Combination of Oral
Rigosertib and Azacitidine in Patients with Myelodysplastic Syndromes
(MDS)", XP002788718, Database accession no. PREV201600270785 ;
& BLOOD, vol. 126, no. 23, December 2015 (2015-12),
57TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-
HEMATOLOGY; ORLANDO, FL, USA; DECEMBER 05 -08, 2015
- D9 KOMROKJI RAMI S. ET AL: "Phase I clinical trial of oral rigosertib in
patients with myelodysplastic syndromes", BRITISH JOURNAL OF
HAEMATOLOGY, vol. 162, no. 4, 21 June 2013 (2013-06-21), pages
517-524, XP055483608

Preliminary remark

- 1 The compound *(E)*-2,4,6-trimethoxystyryl-3-[(carboxymethyl)amino]-4-
methoxybenzylsulphone is also known as ON 01910/ON 01910.Na or as
rigosertib in its sodium salt form.

Re Item IV

Lack of unity of invention

- 2 This Authority considers that the application does not meet the requirements
of unity of invention and that there are two inventions covered by the claims
as follows:
- 2.1 Invention no. (1): **Claims 1-32**
A pharmaceutical composition comprising,

- a) (E)-2,4,6-trimethoxystyryl-3-[(carboxymethyl)amino]-4-methoxybenzylsulphone and pharmaceutically acceptable salts thereof,
- b) basic pre-treated low molecular weight polyethylene glycol;
- c) undiluted pH of about 11.0 to about 14.0; and
- d) less than 5% water or aqueous solution.

A method of treating conditions mediated by abnormal cell proliferation comprising administering an effective amount of the aforementioned pharmaceutical composition to a subject in need thereof.

2.2 Invention no. (2): **Claims 33-36**

A method of treating conditions mediated by abnormal cell proliferation comprising administering an effective amount of (E)-2,4,6-trimethoxystyryl-3-[(carboxymethyl)amino]-4-methoxybenzylsulphone, sodium salt to a patient in need thereof, comprising orally administering a first dose of 840 mg approximately 1-2 hours before breakfast and a second dose of 280 mg about 2 hours after lunch, or administering a first dose of 560 mg approximately 1-2 hours before breakfast and a second dose of 280 - 560 mg about 2 hours after lunch.

3 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

3.1 *A priori*, the "common concept" or "special technical feature" linking together the aforementioned inventions (1) and (2) can be seen in the medical use of use of (E)-2,4,6-trimethoxystyryl-3-[(carboxymethyl)amino]-4-methoxybenzylsulphone (--also known as ON 01910 or rigosertib--).

3.2 The aforementioned "common concept" or "special technical feature" is however already known from the state of the art; see e.g. **D1-D4** below.

D1 (see e.g. c.41, l.20-45 e.g. claim 1) and **D2** (see e.g. c.41, l.63-67) both indicate the possible or potential use of ON 01910.Na in the treatment of cancer.

D3 (see e.g. abstract, p.1657, c.1, §2 and p1658, c.2, §3) discloses the antitumor activity of rigosertib, in patients with advanced solid malignancies, and reports that rigosertib has shown efficacy in patient-derived breast, pancreatic, and myelodysplastic syndrome cancer models.

D4 (see e.g. abstract) discloses the use of ON 01910.Na for treating myelodysplastic syndromes.

- 3.3 In view of **D1-D4**, it follows that the requisite of unity of invention is not complied with, inasmuch as a technical relationship involving one or more of the same or corresponding "special technical feature" in the sense of Rule 13.2 PCT does not exist between the subject-matter of inventions (1) and (2). Hence, *a posteriori*, the inventions or groups of inventions (1) and (2) are considered to relate to separate inventions or groups of inventions which are not so linked as to form a single inventive concept, as required by Rule 13.1 PCT.
- 4 The applicant has paid **one** additional search fee for **invention No. (2)** as defined above.
- 4.1 Consequently, **inventions no. (1) and (2)** have been covered by the supplementary European search report, and an opinion on patentability is given herein for said two inventions.

Re Item V

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

Preliminary remark

- 5 **Claims 28-36** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.
- 5.1 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

INVENTION (1)

Remark

- 6 Due to the clarity objection raised in Re Item VIII below, and for the purpose of this opinion, the feature "*low molecular weight*" in connection "polyethylene glycol (PEG)" has been interpreted as if restricted to "*PEG 200, PEG 300, PEG 400, PEG 600 and PEG 800*", as specified in §[0021] of the description.

- 6.1 The dependent or related **claims 3-9, 11-20 and 24-32** have been read accordingly.

Novelty

- 7 **Claims 1-32** meet the requirements of Art. 33(2) PCT because none of the prior art documents cited in the search report discloses a pharmaceutical composition as specified in the main claim 1 nor any use thereof.

Inventive step

- 8 **Claims 1-32** also meet the requirements of Art. 33(3) PCT for the reasons set out below.

- 8.1 **D1** (see e.g. claim 1) discloses an aqueous composition for parenteral administration comprising: rigosertib, 25% to 47.5% by weight of PEG 300, PEG 400, PEG 600 or PEG 800 and a phosphate buffer; wherein the composition has a pH from about 8 to about 14.

D2 (see e.g. claims 1, 16 and 17) discloses an aqueous composition for parenteral administration comprising: rigosertib, at least 50% by weight of PEG 300, PEG 400, PEG 600 or PEG 800 and a buffer in a pH range of about 7.1 to about 10; including compositions consisting essentially of rigosertib and PEG 400.

D1-D2 (see examples II, VI and V) both exemplify a composition of rigosertib containing 50% PEG 400 in a phosphate buffer with pH=10, as well as a composition of rigosertib formulated in 100% PEG 400; further showing the stability of the latter at different storage conditions. **D1** (see examples VIII and IX) additionally shows that a formulation comprising Rigosertib in 50% PEG 400 plus 50% phosphate buffer with pH=10, exhibits improved storage stability than a comparable formulation comprising rigosertib in 25% PEG 400 plus 75% phosphate buffer with pH=10.

- 8.2 The experimental data of the application (see examples 2-4 and Fig.1) evidence that a composition comprising rigosertib dissolved in PEG 400 pretreated with a NaOH solution to increase the pH to 10-11, said composition optionally further treated with NaOH solution to a target pH of 12.6 (the final product containing 0.9 % water), exhibits:

- improved storage stability (for 1 year at 25°C/60%RH) with regard to a composition comprising rigosertib dissolved in: (a) non-adjusted PEG 400; (b) 50% PEG 400 + 50% phosphate buffer with pH=10; and (c) 25% PEG 400 + 75% phosphate buffer with pH=10; and
 - improved oral bioavailability (in dogs) with regard to a comparable composition comprising rigosertib dissolved in PEG 400 with non-adjusted pH.
- 8.2.1 Said experimental data plausibly substantiate improved storage stability and improved oral bioavailability of rigosertib compositions according to the main **claim 1**, with respect to rigosertib compositions as disclosed in **D1-D2**.
- 8.3 In view of the above and starting from **D1-D2** as closest prior art, the **problem to be solved** by the invention can be regarded as to provide improved rigosertib-based compositions.
- 8.4 The solution proposed in the main **claim 1** involves an inventive step because nothing in **D1 and/or D2** would have prompted the skilled person to prepare a rigosertib composition comprising: a basic pre-treated PEG 300, PEG 400, PEG 600 or PEG 800, less than 5% water or aqueous solution and having an undiluted pH of about 11.0 to about 14.0, with the expectation of solving the referred problem.
- 8.5 Thus, **claim 1**, its dependent **claims 2-27** and the related **claims 28-32** involve an inventive step over the cited prior art.

Industrial applicability

- 9 **Claims 1-32** satisfy the criterion set forth in Art. 33(4) PCT because their subject matter is susceptible of industrial application.

INVENTION (2)

Novelty

- 10 **Claim 33-36** do not meet the requirements of Art. 33(2) PCT because their subject matter is not new (see below).
- 10.1 **D5** (see e.g. claims 1, 4 and 16 (c)) discloses the use of rigosertib for treating cancer refractory to an anticancer agent, by oral administration of rigosertib with an intermittent dosing schedule of 560 mg/280 mg morning and afternoon, respectively for a period of 2-3 weeks. **D5** (see example 7) reports a

study in which patients with relapsed or refractory acute myeloid leukemia (AML) or transformed myeloproliferative neoplasms (MPN) were treated with rigosertib orally, at a dose of 560 mg twice a day continuously for 20 weeks. **D5** (see examples 10-12) discloses: (i) a study in which patients with confirmed solid tumors refractory to standard therapy were treated with escalating doses of oral rigosertib twice daily, including oral rigosertib (560 mg bid) administered either intermittently (2 out of 3 weeks) or continuously; and (ii) studies in which patients with transfusion-dependent lower risk myelodysplastic syndrome (MDS) were treated with 560 mg bid oral rigosertib administered either intermittently (2 out of 3 weeks) or continuously. As indicated in **D5** (see §[0139]), in order to mitigate urinary side effects/toxicity and to minimize nocturnal symptoms of urinary urgency, a strategy was implemented for modification in the dosing schedule of rigosertib to a daily dosing of 560 mg AM and 280 mg PM.

10.1.1 Thus, **D5** destroys the novelty of **claims 33, 35 and 36**.

10.2 Similarly, **D6** (abstract) refers to a phase II study in lower risk transfusion-dependent MDS patients, who were treated with rigosertib (560 mg bid) either intermittently (2 out of 3 weeks) or continuously. It also indicates that, in order to improve urinary tolerability, the dosing was modified to a total daily dose of 840 mg (560 mg am/280 mg afternoon)

10.2.1 Thus, **D6** also destroys the novelty of **claims 33, 35 and 36**.

10.2.2 Both **D7 and D8** (abstracts) disclose a phase II study testing the combination of oral rigosertib and injectable azacitidine in patients with MDS; wherein oral rigosertib was administered twice daily on days 1-21 of a 28-day cycle at a dose of 560 mg qAM and 280 mg qPM, whereas azacitidine was administered at 75 mg/m²/d SC or IV for 7 days starting on day 8.

10.2.3 Hence, **D7 and D8** prejudice the novelty of **claims 33-36**.

Inventive step

11 **Claims 33-36** relate to subject matter which is not new and for which no inventive step can be recognised either. Hence, they do not meet the requirements of Art. 33(3) PCT

11.1 In addition, it is to be noted that **D9** (see e.g. abstract and Fig. 1B) teaches that the mean absolute oral bioavailability of oral rigosertib ranged from 13.9% (fed) to 34.8% (fasting) in 12 patients treated at the 560 mg b.i.d. dose level.

- 11.2 In view of said teachings of **D9**, in combination with those of **D5-D8**, it would be obvious for the skilled person to administer oral rigosertib at doses as specified in claim 33 and in the fasting state; e.g. before breakfast and after lunch.

Industrial applicability

- 12 **Claims 33-36** satisfy the criterion set forth in Art. 33(4) PCT because their subject matter is susceptible of industrial application.

Additional comment

- 13 New claims on the basis of present claims 33-36, but restricted to administration of a pharmaceutical composition according to claim 1 (or claims 1-23) would be considered to form part of invention No. (1). Such claims would meet the requirements of novelty and inventive step for the same reasons as mentioned above for claims 1-28.

Re Item VIII

Certain observations on the international application

- 14 **Claim 1** does not meet the requirements of Art. 6 PCT because the vague feature "low molecular weight" in connection "polyethylene glycol" has no precise meaning and renders the subject matter of said claim unclear.
- 15 The same applies to the dependent or related **claims 3-9, 11-20 and 24-32**.