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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2010/050833	26.01.2010	26.01.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/127 A61K31/198 A61K47/48

Applicant
ACADEMISCH MEDISCH CENTRUM

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 notifed 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.

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Schifferer, Hermann Telephone No. +49 89 2399-7472

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 filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

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 in 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	5-6, 8-9, 14-35, 37-39
	No:	Claims	1-4, 7, 10-13, 36, 40-42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5-6, 8-9, 14-35, 37-39
Industrial applicability (IA)	Yes:	Claims	1-42
	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

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Documents

The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: Huertas-Perez et al., Journal or chromatography, 1157,1-2, XP022131706

D2: US5505954

D3: US5547680

D4: Manosroi-A., Podjanasoonthon-K., Manosroi-J. International Journal or Pharmaceutics. 235, 2002. 61-70, XP002529293

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

2) Novelty - Article 33 (1) and (2) PCT

2.1) D1 discloses the antifibrinolytic agent, tranexamic acid, being incorporated in large unilamellar vesicles from DPPC and DSPE - PEG at a 96:4 molar ratio. It was noted that tranexamic acid would be considered as a candidate adjuvant drug for site - specific pharmaco - laser therapy of port-wine stains.

In D2 and D3 ophthalmic gel formulations containing 30 % epsilon aminocaproic acid are described which may be incorporated into liposomes composed of soya lecithin, phosphatidyl choline and other compounds.

D4 shows liposome formulations comprising tranexamic acid, hydrogenated soya phosphatidylcholine and cholesterol, positive (stearylamine) or negative (dicetyl phosphate) charged lipid. Typical examples include a 7:2:1 molar ratio of hydrogenated soy phosphatidylcholine/cholesterol/dicetyl phosphate entrapped with 10 % tranexamic acid liposome.

The indications related to local or systemic fibrinolysis are well known from the products Cyklokapron on the US and European market and Transamin on the Asian market. First marketing authorization in the UK was on February 9th, 1987.

2.2) D1-D4 do not disclose the use of photosensitizers and of targeting molecules, as well as not clinical instruments with said composition.

2.3) In the light of D1-D4, the subject-matter of claims 1-4,7,10-13,36,40-42 does not seem to be novel, thus not fulfilling the criteria of Articles 33(1) and (2) PCT.

2.4) In the light of D1-D4, the subject-matter of claims 5,6,8,9,14-35,37-39 could be considered new in the sense of Article 33(1) and (2) PCT, since not being disclosed in D1-D4.

3) Inventive Step - Article 33 (1) and (3) PCT

3.1) The problem posed in the present application was the development of an alternative modality to be used in conjunction with conventional photocoagulation which improves lesional clearance rates by optimizing the occlusion of target blood vessels.

The solution, according to the Applicant, was a drug delivery system for use in the treatment of vascular and vessel - related pathologies, comprising a drug delivery platform that comprises at least one compound capable of exerting an effect on the formation and/or maintenance of a thrombus in the vessel to be treated.

D1 which can be regarded as closest prior art discloses the antifibrinolytic agent, tranexamic acid, being incorporated in large unilamellar vesicles from DPPC and DSPE - PEG at a 96:4 molar ratio. It was noted that tranexamic acid would be considered as a candidate adjuvant drug for site - specific pharmaco - laser therapy of port-wine stains.

D1 differs from present application, since it does not disclose the inclusion of photosensitizers and targeting molecules. Additionally it lacks the suggestion of liposome systems with all concrete methods for steric stabilization, purified and/or recombinant antiplasmin or fibrinolysis inhibitors or inhibitors of tissue plasminogen activators. Also clinical instruments for facilitating drug release from the drug delivery systems and/or photosensitization are not described.

Surprising or unexpected effects are not given for those issues in present application.

3.2) The subject-matter of claims 5,6,8,9,14-35,37-39 seems to be obvious to a person skilled in the art due to general textbook knowledge. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

VIII Certain observations on the international application (clarity)

1.1) Claims 1 / 2-42 in part do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the subject - matter in terms of the result to be achieved, namely by defining the active compounds as being capable of exerting an effect on the formation and/or maintenance of a thrombus in the vessel to be treated. Such a definition is only allowable under the conditions elaborated in the Guidelines for the Examination in the European Patent Office, C - III, 4.10. In this instance, however, such a formulation is not allowable because it appears possible to define the subject - matter in more concrete terms, viz. in terms of how the effect is to be achieved.

1.2) The expression "vascular and vessel-related pathologies" in claim 40 is not considered sufficiently clear, since the type of the disease, of the condition meant is not precisely specified. Therefore, doubts arise on the scope of the invention and therefore, the application lacks clarity (Article 6 PCT).

1.3) The expression of a "cell ghost" in claim 2 does not seem to be sufficiently clear according to Article 6 PCT.