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CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
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kind of regional protection available): ARIPO (BW, GH,

(54) Title: INHALABLE COMPOSITIONS COMPRISING MACROCYCLIC IMMUNOSUPPRESSANTS

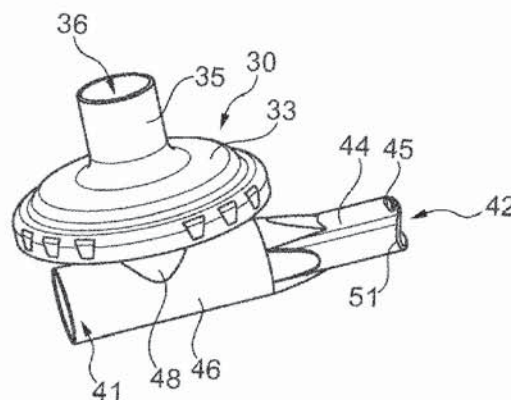


Fig. 3

(57) Abstract: The present disclosure relates to a pharmaceutical composition comprising an inhalable immunosuppressive macrocyclic active ingredient for use in the prevention or treatment of a pulmonary disease or condition in a subject, wherein the pharmaceutical composition is administered to the subject by inhalation in form of an aerosol, and wherein the aerosol is generated by nebulization of the pharmaceutical composition using a nebulizer (100), the nebulizer comprising: a) an aerosol generator (101) comprising: - a fluid reservoir (103) for holding the pharmaceutical composition or an interface configured to connect a fluid reservoir, and - a vibratable membrane (110) having a plurality of apertures, the apertures being adapted to produce an aerosol comprising droplets having a mass median aerodynamic diameter (MMAD) of up to about 15.4 µm as measured with a 0.9 % (w/v) aqueous solution of sodium chloride; b) a chamber (105) for temporarily accommodating the aerosol generated by the aerosol generator (101), the chamber having an inner lumen with a volume in the range of from about 50 to about 150 ml; and c) a mouthpiece (40) for delivering the aerosol supplied by the nebulizer (100) to the subject, the mouthpiece having an exhalation filter (30).

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

To: Kurt Schellhaas Pharma Patents International AG Leonhardsgraben 52 4051 Basel SUISSE		Date of mailing (day/month/year) 02.11.2020	
Applicant's or agent's file reference BRH18P01PC1		IMPORTANT NOTIFICATION	
International application No. PCT/EP2019/066872	International filing date (day/month/year) 25.06.2019	Priority date (day/month/year) 27.06.2018	
Applicant Breath Therapeutics GmbH			
1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application. 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices. 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices. 4. REMINDER The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301). Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide. The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.			
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized Officer Brell, Eva Tel. +49 89 2399-6724	



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BRH18P01PC1	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2019/066872	International filing date (day/month/year) 25.06.2019	Priority date (day/month/year) 27.06.2018	
International Patent Classification (IPC) or national classification and IPC INV. A61K38/13			
Applicant Breath Therapeutics GmbH			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>10</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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			
Date of submission of the demand 10.03.2020		Date of completion of this report 02.11.2020	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Schüle, Stefanie Telephone No. +49 89 2399-4865 	

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-61 as originally filed

Claims, Numbers

1-30 filed with the demand for preliminary international examination

Drawings, Sheets

1-3 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2019/066872

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 11.05.2020 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-30</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-30</u>
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

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

1 DOCUMENTS

Reference is made to the following documents:

D1 US 2013/177626

D2 WO 2016/146645

D3 WO 98/00111

2 REMARK

The applicant has not filed a reply to the written opinion dated 20.05.2020, so that the objections raised in this opinion are still valid for the International Preliminary Report on Patentability.

3 NOVELTY (Art. 33(2) PCT)

3.1 The set of claims as filed in reply to the international search opinion is considered to meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-30 is new in the sense of Article 33(2) PCT.

3.2 D1 discloses an aerosol for inhalation comprising cyclosporin in liposomally solubilised form (claim 52). The composition is administered with an electronic vibrating membrane nebuliser (claim 54). The nebuliser seems to be the same and the features of the volume of the chamber and the MMAD is implicitly disclosed. The composition is used for the treatment of bronchiolitis obliterans (claim 53). However, D1 does not disclose that the composition comprises *"at least one disaccharide selected from the group consisting of saccharose, lactose and trehalose in the range of from about 5 to about 15 wt.-%, based on the total weight of the pharmaceutical composition. The same applies to D2, which however refers to sucrose as lyoprotectant, but does not disclose the amount of it"*.

4 INVENTIVE STEP (Art. 33(3) PCT)

- 4.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-30 does not involve an inventive step in the sense of Article 33(3) PCT.
- 4.2 The document D2 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses an aerosol for inhalation of liposomal cyclosporin (example 1). Sucrose is added as lyoprotectant and the formulation is lyophilised. Before nebulization, the composition is dissolved (example 2).
- 4.3 The subject-matter of claim 1 therefore differs from this known D2 in that the amount of sucrose is between 5 and 15%.
- 4.4 In the absence of any surprising technical effect shown for the difference, the problem to be solved by the present invention may therefore be regarded as provision of an alternative composition for inhalation.
- 4.5 The applicant argued that D2 was absolutely silent with regard to the specific amount in which such lyoprotective and/or bulking agent should be added to achieve the lyoprotection and/ or bulking of the dried residue. The applicant further stated that large amounts of a disaccharide tended to change the physical characteristics, for example with regard to the viscosity and/ or adhesiveness. The skilled person would therefore not consider to include a significant amount of a lyoprotective sugar.
- 4.6 However, the examiner is of the opinion that D2 already discloses the use of sucrose as lyoprotectant and even if not disclosed, the amount appears to be in a range which would be used by the skilled person. The applicant has not proven that the skilled person would not work in the claimed range. Furthermore, in particular as no special technical effect was shown for this claimed range. The use of sucrose as excipient for inhalation is well-known and therefore, the skilled person would have found by trial and error the adequate amount of lyoprotectant for a composition intended for inhalation.
- 4.7 The same reasoning applies for the subject-matter of claim 2-30 which are also not considered inventive.

5 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

The subject-matter of claims 1-30 is industrial applicable according to Art. 33(4) PCT.

Pharma Patents International AG · ☒ Leonhardsgraben 52 · 4051 Basel (Switzerland)

European Patent Office
80298 München
GERMANY

Application number: PCT/EP2019/066872
Filing Date: 2019-06-25
Applicant(s): Breath Therapeutics GmbH
Our reference: BRH18P01PC1

Date: 10 March 2020

**Demand for International Preliminary Examination according to Art. 31 PCT –
Amended claims according to Art. 34 PCT**

I. International Preliminary Examination according to Art. 31 PCT is herewith requested in connection with the above-identified international patent application.

II. Amended claims 1 to 30 are herewith provided according to Art. 34 PCT which shall form the basis for the requested International Preliminary Examination.

II.1 Amended claims 1 to 30 differ from claims 1 to 30 as originally filed in that

- a) the subject matter of original claim 17 has been introduced into independent claims 1 and 28, respectively;
- b) in claim 16 as originally filed the feature “*at least one disaccharide selected from the group consisting of saccharose, lactose and trehalose*” has been deleted;
- c) in claim 17 as originally filed the feature “*of from about 5 to about 15 wt.-%*” has been deleted; and
- d) in claims 11, 15 and 18 the back-references have been adapted; in claim 24 the expression ‘item’ has been replaced by the expression ‘claim’.

II.2 Basis for the above-described amendments can be found in claims 1 and 28 as originally filed in connection with claim 17 as originally filed on page 19, l. 9 to 17 and page 4, l. 26 to page 5, l. 3 of the application as filed.

II.3 No new matter has been added. The applicant further notes that no subject matter of the present application is abandoned and any subject matter exchanged or replaced by the present amendments may be reintroduced and further pursued at a later stage of the proceedings in connection with the present international patent application or in connection with national or regional patent applications or divisional applications derived therefrom.

III. With regard to the findings of the International Searching Authority (ISA) as reported in the International Search Report (ISR) dated Oct. 14, 2019 the Applicant wishes to comment as follows:

III.1 Novelty (Art. 33(2) PCT):

III.1.1 According to item 2 of the above-referenced ISR the subject matter of claims 1 to 30 is found not to fulfill the requirements of Art. 33(2) PCT. More specifically, the subject matter of claims 1 to 16 and 18 to 30 as originally filed is found to be anticipated by reference document D1 (US 2013/177626 A1; Keller et al.). Furthermore, the subject matter of claims 1 to 30 as originally filed is found to be anticipated by reference document D2 (WO 2016/146645 A1; Knoch M.).

III.1.2 On the basis of claims 1 to 30 as currently amended and as submitted herewith the Applicant respectfully submits that the subject matter of the present application fulfills the requirements of Art. 33(2) PCT for **at least** the reasons that

- reference document D1 does not disclose a pharmaceutical composition for inhalation comprising a disaccharide selected from the group of saccharose, lactose and trehalose as acknowledged by the ISA in the ISR; and
- reference document D2 does not disclose a pharmaceutical composition for inhalation or a kit comprising such a pharmaceutical composition and a nebulizer wherein the pharmaceutical composition comprises a disaccharide selected from the group consisting of saccharose, lactose or trehalose **in an amount of from about 5 to about 15 wt.% based on the total weight of the pharmaceutical composition.**

III.1.3 Accordingly, it is respectfully submitted that in view of the prior art documents as presently on file the subject matter of claims 1 to 30 as presently amended fulfills the requirements of Art. 33(2) PCT.

III.2 Inventive step (Art. 33(3) PCT):

III.2.1 Based on the reasoning as outlined above and solely for the purpose of International Preliminary Examination as requested herewith, reference document D2 is considered as closest prior art.

III.2.2 In view of reference document D2, the person of ordinary skill in the art would have had no hint or motivation to include a disaccharide selected from the group consisting of saccharose, lactose or trehalose **specifically in an amount of about 5 to about 15 wt.-%** based on the total weight of the pharmaceutical composition.

III.2.3 Reference document D2 seems to disclose that saccharose and a broad variety of other sugars or sugar alcohols might be used as a *“lyoprotective and/or bulking agent”*. (D2, page 9, l. 18 to 21) The document, however, is absolutely silent with regard to the specific amount in which such lyoprotective and/or bulking agent should or can be added to achieve the desired result, presumably lyoprotection and/or bulking of the dried residue. In Example 2 also, (D2, page 19, l. 17 to 20) - assumingly corresponding to “Example 4” as referred to in the Written Opinion accompanying the ISR - no information or teaching is given at all with regard to the amount of sucrose that may be added as a lyoprotectant. It is merely stated: *“Sucrose was added as a lyoprotectant to the formulation described in Example 1.”*

III.2.3 In this context it should be noted that the pharmaceutical composition for use according to the present invention is to be applied by **“inhalation in the form of an aerosol”** (see claim 1). Furthermore, it should be pointed out, that large amounts of a disaccharide, especially when present in a formulation for inhalation like the formulations for use according to the present invention, tend to change the physical characteristics of such a formulation significantly, for example with regard to the viscosity and/or adhesiveness of such a composition.

III.2.4 Furthermore, it should be noted that the person of ordinary skill in the art when starting from reference document D2 as closest prior art would consider using an inhaler with a vibratable membrane for the aerosolization/nebulization of the present pharmaceutical compositions. Based on the aforementioned characteristics of a formulation comprising a significant amount of a lyoprotective sugar and further considering that such pharmaceutical compositions might bear the risk of clogging the (tiny) apertures of the vibrating membrane of the nebulizer, however, the skilled artisan **would** definitely **not** have considered to include a significant amount of a lyoprotective sugar.

III.2.5 Nonetheless, it was surprisingly found by the inventors that a pharmaceutical composition for use according to the present invention can be nebulized and effectively administered to a patient when containing a disaccharide selected from the group consisting of saccharose, lactose and trehalose in a significant amount within the range of from about 5 to about 15 wt.-% based on the total weight of the pharmaceutical composition.

III.2.6 Further, it was surprisingly found that only if used in combination with a specifically adapted nebulizer having an aerosol generator with a chamber having a volume from about 50 to about 150 ml **and in combination therewith** a vibratable membrane with apertures being adapted to produce an aerosol comprising droplets having a mass median aerodynamic diameter (MMAD) of up to about 4.0 μm as measured with a 0.9 % (w/v) aqueous solution of sodium chloride it is possible to effectively aerosolize such a composition.

III.2.7 On this basis, it is respectfully submitted that the subject matter of independent claims 1 and 28 as presently amended as well as of all claims directly or indirectly depending thereon fulfills the requirements of Art 33(3) PCT.

/Kurt Schellhaas/
European Patent Attorney

Pharma Patents International AG (Association No. 688)

Enclosure(s)

- Amended claims 1 to 30 (clean and marked version)

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AMENDED CLAIMS:

1. A pharmaceutical composition comprising an inhalable immunosuppressive
5 macrocyclic active ingredient for use in the prevention or treatment of a
pulmonary disease or condition in a subject,

wherein the pharmaceutical composition is administered to the subject by
inhalation in form of an aerosol, and

wherein the aerosol is generated by nebulization of the pharmaceutical
10 composition using a nebulizer (100), the nebulizer comprising:

- a) an aerosol generator (101) comprising:

- a fluid reservoir (103) for holding the pharmaceutical composition or
an interface configured to connect a fluid reservoir, and
- a vibratable membrane (110) having a plurality of apertures, the
15 apertures being adapted to produce an aerosol comprising droplets
having a mass median aerodynamic diameter (MMAD) of up to about
4.0 μm as measured with a 0.9 % (w/v) aqueous solution of sodium
chloride;

- b) a chamber (105) for temporarily accommodating the aerosol generated by the
20 aerosol generator (101), the chamber having an inner lumen with a volume in
the range of from about 50 to about 150 ml; and

- c) a mouthpiece (40) for delivering the aerosol supplied by the nebulizer (100)
to the subject, the mouthpiece having an exhalation filter (30); and

wherein the composition comprises at least one disaccharide selected from the
25 group consisting of saccharose, lactose and trehalose in the range of from about 5
to about 15 wt.-%, based on the total weight of the pharmaceutical composition.

2. The pharmaceutical composition for use according to claim 1, wherein the
pulmonary disease or condition is selected from the group consisting of asthma,
refractory asthma, chronic obstructive bronchitis, parenchymal, fibrotic and
30 interstitial lung diseases and inflammations, bronchiolitis obliterans (BOS), and

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acute and chronic organ transplant rejection reactions after lung transplantations and the diseases resulting therefrom.

3. The pharmaceutical composition for use according to any of the preceding claims, wherein the pulmonary disease or condition is bronchiolitis obliterans (BOS)
5 grade I or higher, specifically BOS grade I or II, especially BOS grade I.

4. The pharmaceutical composition for use according to any of the preceding claims, wherein the inhalable immunosuppressive active ingredient is cyclosporine A.

5. The pharmaceutical composition for use according to any of the preceding claims, wherein the inhalable immunosuppressive active ingredient is present in
10 liposomally solubilized form (L-CsA).

6. The pharmaceutical composition for use according to any preceding claim, wherein the composition is a liquid composition comprising an aqueous liquid vehicle.

7. The pharmaceutical composition for use according to any preceding claim,
15 wherein the aqueous liquid composition comprising the inhalable immunosuppressive macrocyclic active ingredient in liposomally solubilized form is obtained by reconstitution of a lyophilisate comprising the immunosuppressive macrocyclic active ingredient and liposome forming structures.

8. The pharmaceutical composition for use according to claim 7, wherein the
20 liposome-forming structures comprise a bilayer membrane formed of a membrane-forming substance selected from the group of phospholipids.

9. The pharmaceutical composition for use according to claim 8, wherein the membrane-forming substance selected from the group of phospholipids is a mixture of natural phospholipids.

10. The pharmaceutical composition for use according to claim 8 or 9, wherein the
25 membrane-forming substance selected from the group of phospholipids is a lecithin containing unsaturated fatty acid residues.

11. The pharmaceutical composition for use according to any of claims 8 to 10, wherein the membrane forming substance selected from the group of

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phospholipids is a lecithin selected from the group consisting of soy bean lecithin, Lipoid S75, Lipoid S100, Phospholipon® G90, 100 or a comparable lecithin.

12. The pharmaceutical composition for use according to any preceding claim, wherein the composition further comprises at least one solubility-enhancing substance selected from the group of non-ionic surfactants.

13. The pharmaceutical composition for use according to claim 12, wherein the at least one non-ionic surfactant is selected from the group of polysorbates.

14. The pharmaceutical composition for use according to claim 12 or 13, wherein the solubility-enhancing substance selected from the group of non-ionic surfactants is polysorbate 80.

15. The pharmaceutical composition for use according to claim 13 or 14, wherein the weight ratio of phospholipid to polysorbate is selected in the range of from about 15 : 1 to about 9 : 1, preferably between from about 14 : 1 to about 12 : 1, for example, about 13 : 1.

16. The pharmaceutical composition for use according to any preceding claim, wherein the composition comprises saccharose.

17. The pharmaceutical composition for use according to any preceding claim, wherein the composition comprises at least one disaccharide selected from the group consisting of saccharose, lactose and trehalose, preferably saccharose, in the range of from about 7.5 to about 12.5 wt.-%, based on the total weight of the pharmaceutical composition.

18. The pharmaceutical composition for use according to any of claims 7 to 17, wherein the inhalable immunosuppressive macrocyclic active ingredient is at least partially incorporated (or intercalated) in the bilayer membrane of the liposome-forming structures.

19. The pharmaceutical composition for use according to any preceding claim, wherein the vibratable membrane (110) has from about 100 to about 400 apertures per mm².

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20. The pharmaceutical composition for use according to any preceding claim, wherein the plurality of apertures of the vibratable membrane (110) have a tapered shape narrowing towards the aerosol release side of the vibratable membrane.
- 5 21. The pharmaceutical composition for use according to any preceding claim, wherein the apertures of the vibratable membrane have an exit diameter in the range of from about 1.5 μm to about 3.0 μm as measured by scanning electron microscopy (SEM).
- 10 22. The pharmaceutical composition for use according to any preceding claim, wherein the inhalable immunosuppressive macrocyclic active ingredient is delivered to the lungs (or the lung) of the subject in an amount (Delivered dose, DD) of at least 70%, more specifically in an amount in the range of from about 70% to about 80% of the amount administered to the subject.
- 15 23. The pharmaceutical composition for use according to any preceding claim, wherein the aerosol administered to the patient comprises droplets and wherein from about 60 % to about 95 % of the total number of droplets have a diameter of up to 5 μm (as measured by laser diffraction or by a multistage cascade impactor as described above) when measured with a aqueous composition comprising L-CsA in concentration of 4 mg/mL.
- 20 24. The pharmaceutical composition for use according to any preceding claim, wherein the inhalable immunosuppressive macrocyclic active ingredient is administered to the subject at a total output rate (TOR) of at least 200 mg/min, more specifically at a total output rate in the range of from about 200 to about 250 mg/min.
- 25 25. The pharmaceutical composition for use according to any preceding claim, wherein the amount of the inhalable immunosuppressive macrocyclic active ingredient exhaled by the subject is up to 10%, more specifically from about 4% to about 8% of the total amount of active ingredient administered to the subject.
- 30 26. The pharmaceutical composition for use according to any preceding claim, wherein 1 mL of the pharmaceutical composition comprising an inhalable

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immunosuppressive macrocyclic active ingredient is aerosolized (nebulized) within a period of up to about 5 min.

27. The pharmaceutical composition for use according to any preceding claim, wherein the mouthpiece (40) comprises:

5 a body (46) defining a fluid path (47) from an inlet port (41) connectable to the nebulizer (100) to an inhalation opening (42) to be received in the mouth of the user; and

10 an exhalation filter (30) having a filter base (31) in fluid communication with the fluid path (47), a filter top (33) detachably connected to the filter base (31) and a filter material (32) provided between the filter base (31) and the filter top (33), wherein the filter top (33) has an exhalation opening (36) cooperating with a one-way valve (39) allowing exhaustion of fluid from the fluid path (47) through the filter material (32) to the outside of the mouthpiece (40) upon exhalation of a patient through the inhalation opening;

15 wherein the body (46) and the filter base (31) are an integrated one-piece unit.

28. A kit comprising

20 – a pharmaceutical composition comprising an inhalable immunosuppressive macrocyclic active ingredient for use in the prevention or treatment of a pulmonary disease or condition in a subject;

wherein the composition comprises at least one disaccharide selected from the group consisting of saccharose, lactose and trehalose in the range of from about 5 to about 15 wt.-%, based on the total weight of the pharmaceutical composition; and

25 – a nebulizer (100), the nebulizer comprising:

a) an aerosol generator (101) comprising:

– a fluid reservoir (103) for holding the pharmaceutical composition or an interface configured to connect a fluid reservoir, and

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- a vibratable membrane (110) having a plurality of apertures, the apertures being adapted to produce an aerosol comprising droplets having a mass median aerodynamic diameter (MMAD) of up to about 4.0 μm as measured with a 0.9 % (w/v) aqueous solution of sodium chloride;

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b) a chamber (105) for temporarily accommodating the aerosol generated by the aerosol generator (101), the chamber having an inner lumen with a volume in the range of from about 50 to about 150 ml; and

c) a mouthpiece (40) for delivering the aerosol supplied by the nebulizer (100) to the subject, the mouthpiece having an exhalation filter (30).

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29. The kit according to claim 28, wherein the pharmaceutical composition comprising an inhalable immunosuppressive macrocyclic active ingredient for use in the prevention or treatment of a pulmonary disease or condition in a subject is provided in form of a preformed liquid aqueous composition.

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30. The kit according to claim 28, wherein the pharmaceutical composition comprising an inhalable immunosuppressive macrocyclic active ingredient for use in the prevention or treatment of a pulmonary disease or condition in a subject is provided in form of a lyophilisate comprising the inhalable immunosuppressive macrocyclic active ingredient and a sterile liquid aqueous carrier liquid for the reconstitution of the lyophilisate to form a liquid pharmaceutical composition.

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