

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/IB2024/051087

International filing date (day/month/year)
06.02.2024

Priority date (day/month/year)
09.02.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/12 A61K39/145 A61P31/16 C07K14/005 C12N15/86

Applicant
PFIZER 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 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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 43*bis*.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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-19</u>
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

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

Item V

V.1 Reference is made to the following documents:

- D1 WO 2020/035609 A2 (GLAXOSMITHKLINE BIOLOGICALS SA [BE]) 20 February 2020 (2020-02-20)
- D2 Diletta Magini ET AL: "Self-Amplifying mRNA Vaccines Expressing Multiple Conserved Influenza Antigens Confer Protection against Homologous and Heterosubtypic Viral Challenge", PLOS ONE, vol. 11, no. 8, 1 January 2016 (2016-01-01), page e0161193, XP055397457
- D3 WO 2022/118226 A1 (SEQIRUS INC [US]) 9 June 2022 (2022-06-09)
- D4 Liu Yi ET AL: "Messenger RNA translation enhancement by immune evasion proteins: a comparative study between EKB (vaccinia virus) and NS1 (influenza A virus)", SCIENTIFIC REPORTS, vol. 9, no. 1, 1 December 2019 (2019-12-01), page 11972, XP055907045
- D5 CHANG CHENG ET AL: "Self-amplifying mRNA bicistronic influenza vaccines raise cross-reactive immune responses in mice and prevent infection in ferrets", MOLECULAR THERAPY-METHODS & CLINICAL DEVELOPMENT, vol. 27, 3 October 2022 (2022-10-03), pages 195-205, XP093088987
- D6 WO 2024/013625 A1 (PFIZER [US]) 18 January 2024 (2024-01-18) (**Pdoc**)

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes an immunogenic composition comprising (i) a first self-replicating RNA molecule encoding a polypeptide comprising a first antigen derived from influenza virus and (ii) a second self-replicating RNA molecule encoding a polypeptide comprising a second antigen derived from influenza virus, wherein both antigens are derived from different strains (bicistronic SAM vaccines). Said srRNA are comprised in LNPs. (see Examples 1-5, Example 5: tetravalent vaccine)

Document D2 describes that self-amplifying mRNA (SAM) vectors expressing influenza NP, M1, and NP-M1 delivered with lipid nanoparticles (LNPs) induced robust polyfunctional CD4 T helper 1 cells and cytotoxic CD8 T cells (abstract). Mono- and bicistronic self-amplifying RNA comprising a m7G-ppp cap, a 5'UTR, non-structural nsp1 to nsp4, one (in the monocistronic RNA molecule) or two (in the bicistronic RNA molecule) subgenomic promoter(s), coding sequences for one or two influenza proteins (NP, M1, NP-M1), a 3'UTR and a polyA tail (Figure 1).

Document D3 describes bicistronic or tricistronic saRNAs comprising a gene for influenza virus HA under control of a first subgenomic promoter and second gene derived from influenza virus under the control of a second subgenomic promoter. The saRNAs are derived from VEEV strain TC-83:SEQ 10 (NSP1-4.SGP.H5.SGP.N1, construct F548). The saRNAs are formulated as LNPs (p. 91 I. 5-29) and induce antigen specific T cell responses (Examples 3, 7, 9, Figure 6, Tables 9-12).

Document D4 describes that influenza NS1 enhances mRNA translation and suppresses interferon production thereby prevent innate immune responses (immune evasion protein) (abstract). D4 reports that

By co-delivery of mRNA encoding immune evasion proteins and mRNA-of-interest, immune responses triggered during transfection are effectively suppressed, and translation of mRNA-of-interest is greatly enhanced. (p. 1 3rd paragraph)

Document D5 describes bicistronic saRNA for HA and NA (H5N1, H3N2) using a second subgenomic promoter, TC-83 backbone with chimeric 3'UTR from Sindbis virus, capped saRNA, polyA of unknown length. Furthermore, an LNP formulation in ionizable lipid, DSPC, PEG-DMG, and cholesterol is disclosed (see entire document).

V.2.2 With respect to claims 1-19

None of the cited prior art documents describes the subject-matter of independent claim 1, i.e. a composition comprising a self-amplifying RNA encoding an influenza virus antigen and a RNA molecule encoding an influenza non-structural protein (e.g. NS1). Therefore, claims 1-19 are considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 1-9 and 15-19

The subject-matter of claims 1-9, 15-19 differs from each of the closest prior art documents D1-D3 or D5 in that the self-amplifying RNA encoding an antigen derived from influenza virus is combined with a second RNA molecule encoding an influenza non-structural protein.

The technical effect based on said difference is not apparent from the application as originally filed, since the application does not provide any experimental data for a non-structural protein other than NS1.

The technical problem to be solved may be regarded as providing an alternative composition comprising a self-amplifying RNA molecule.

The mere provision of an alternative can only be regarded as demonstrating inventive step when the alternative provides some sort of technical advantage, otherwise the specific choice is merely an arbitrary selection of one among a number of equally viable known alternatives.

Hence the subject-matter of claims 1-9 and 15-19 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claims 10-14

The subject-matter of claims 10-14 differs from each of the closest prior art documents D1-D3 or D5 in that the self-amplifying RNA encoding an antigen derived from influenza virus is combined with a second RNA molecule encoding an influenza NS1.

The technical effect based on said difference is an enhanced mRNA expression and cell-viability, and a suppression of innate immune response.

The technical problem to be solved may be regarded as providing an (immunogenic) composition showing improved properties.

The skilled person starting from each of D1-D3 or D5 searching for an immunogenic composition showing improved properties certainly knows the teaching of D4 describing the influence of NS1 on antigen expression and prevention of innate immune response in the context of mRNA vaccination. The skilled person would combine a self-amplifying RNA vaccine with the beneficial effect of RNA encoding NS1 on mRNA expression and innate immune response.

Hence the subject-matter of claims 10-14 is not inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-19

The subject-matter of claims 1-19 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 18 and 19

The subject-matter of claims 18 (see item VIII.1 below) and 19 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 18 and 19 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. 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.

Patentability, in particular novelty and inventive step, of claims 18 and 19 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Item VI

VI.1 With respect to documents D6

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited document D6 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D6 could be relevant to the question of novelty

Item VIII

VIII.1 With respect to claim 18

Claim 18 reads

A method of expressing a target mRNA in a cell, comprising delivering to the cell a composition according to any one of claims 1-17.

Said cell may be in an organism. Therefore, claim 18 refers to an in vivo method.

VIII.2 With respect to claim 17

Claim 17 reads

An immunogenic composition according to any one of claims 1-16.

Claim 17 appears to be redundant, since the composition of claims 1-16 is an immunogenic composition (Article 6 PCT).

VIII.3 With respect to claim 1

Claim 1 reads

A composition comprising a first RNA molecule encoding a target or gene of interest derived from influenza virus and a second RNA molecule encoding an influenza non-structural (NS1) protein, wherein the first polynucleotide is a self-amplifying RNA. (emphasis added)

Claim 1 does not mention a "first polynucleotide", it refers to a "first RNA molecule" (Article 6 PCT).

VIII.4 With respect to claims 2, 5, 6,

Claims 2, 5, 6 refer to modified nucleotide(s) without defining the nature of said modification. Therefore, claims 2, 5, 6 are unclear in the sense of Article 6 PCT.

VIII.5 With respect to claim 7

Claim 7 reads

The composition according to claim 7 [...]

Therefore, claim 7 does not meet the requirements of Article 6 PCT.

VIII.6 With respect to claim 10

Claim 10 reads

The composition according to any of claims 1 - 9, wherein the influenza NS1 is selected from the group consisting of a type A influenza virus NS1, a type B influenza virus NS1, a type C influenza virus NS1, and a variant thereof. (emphasis added)

The variant of NS1 is not defined (Article 6 PCT).

VIII.7 With respect to claim 13

Claim 13 reads

The composition according to any of claims 1-12, wherein expression of the target mRNA is increased relative to the expression of the target mRNA in the absence of the nucleic acid molecule encoding the influenza NS1 protein.

It appears that claim 13 discloses the technical effect of the combination defined in claim(s) 1(-12). Either an essential feature is missing in claim(s) 1(-12) or claim 13 is redundant (Article 6 PCT).

VIII.8 With respect to claims 1-9, and 15-19

Claim 1 reads

A composition comprising a first RNA molecule encoding a target or gene of interest derived from influenza virus and a second RNA molecule encoding an influenza non-structural (NS1) protein, wherein the first polynucleotide is a self-amplifying RNA. (emphasis added)

Features written within brackets are optional and do not limit the scope of a claim. Therefore, claim 1 refers to "an influenza non-structural protein". Influenza virus encodes for several non-structural proteins (NSPs), e.g., NS1, NS2, NS3, PB1-F2, PB1-N40, PA-N155, PA-N182, M42 and PA-X. The application describes a composition comprising an RNA molecules encoding NS1. Therefore, a composition comprising one of the other NSPs is not supported by the application as originally filed (Article 6 PCT).