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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM,

DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

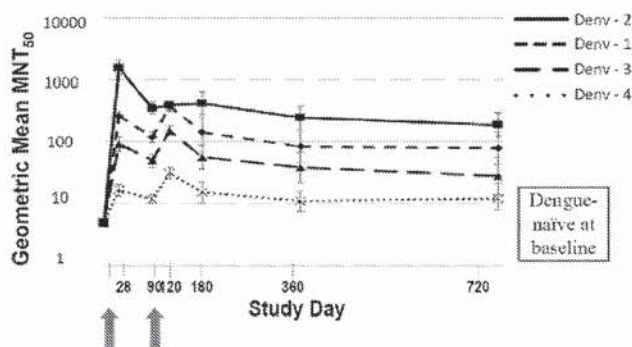
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

- with international search report (Art. 21(3))

- (54) Title: COMPOSITIONS AND METHODS OF VACCINATION AGAINST DENGUE VIRUS IN CHILDREN AND YOUNG ADULTS

FIG. 13B



- (57) Abstract: Embodiments herein concern compositions, methods, and uses for inducing an immune response to all four dengue virus serotypes in a child or young adult from about 1 year to about 20 years of age. Some embodiments concern compositions that can include, but are not limited to, dengue virus chimeras that, either alone or in combination with other constructs, can be used in a vaccine composition against all four dengue virus serotypes. In certain embodiments, compositions can include constructs of more than one serotypes of dengue virus, such as dengue-1 (DEN-1) virus, dengue-2 (DEN-2) virus, dengue-3 (DEN-3) virus and/or dengue-4 (DEN-4) virus, at various concentrations or ratios in order to improve protection from infection in children and young adults. In certain embodiments, viruses of the formulations are limited to dengue virus serotypes. Other embodiments concern methods of administering immunogenic compositions against dengue virus that can include chimeric dengue constructs and live, attenuated dengue viruses using single, dual or other regimens.

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

HUENGES, Martin
Maiwald Patentanwalts - und
Rechtsanwaltsgesellschaft mbH
Elisenhof
Elisenstrasse 3
80335 München
ALLEMAGNE

Date of mailing (day/month/year) 02 October 2018 (02.10.2018)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 478484-265	
International application No. PCT/IB2017/052160	International filing date (day/month/year) 13 April 2017 (13.04.2017)

1. The following indications appeared on record concerning:		
☐ the applicant	☐ the inventor	☐ the agent
☐ the common representative		
Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
☐ the person	☐ the name	☐ the address
☐ the nationality		
☐ the residence		
Name and Address BOSLEGO, John 7917 Springer Road Bethesda, MD 20817 United States of America	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	
3. Further observations, if necessary: The person identified in Box 2 has been added as inventor for all designated States.		
4. A copy of this notification has been sent to:		
☐ the receiving Office	☒ the International Preliminary Examining Authority	
☒ the International Searching Authority	☐ the designated Offices concerned	
☐ the Authority(ies) specified for supplementary search	☒ the elected Offices concerned	
	☐ other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Diot Sylvie
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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 478484.265	FOR FURTHER ACTION		See Form PCT/IPEA/416																
International application No. PCT/IB2017/052160	International filing date (<i>day/month/year</i>) 13.04.2017	Priority date (<i>day/month/year</i>) 13.04.2016																	
International Patent Classification (IPC) or national classification and IPC INV. A61K39/12																			
Applicant Takeda Vaccines, Inc.																			
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>10</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>13</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. ☐ (<i>sent to the International Bureau only</i>) 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: <table style="width: 100%; border: none;"> <tr> <td style="width: 10%;">☒ Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td>☐ Box No. II</td> <td>Priority</td> </tr> <tr> <td>☒ Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td>☐ Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td>☒ Box No. V</td> <td>Reasoned conclusion under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td>☐ Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td>☐ Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td>☒ Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>				☒ 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 conclusion 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
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☒ Box No. VIII	Certain observations on the international application																		
Date of submission of the demand 13.02.2018		Date of completion of this report 15.08.2018																	
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 Marinoni J-C Telephone No. +49 89 2399-8563																	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2017/052160

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

1-70 as originally filed

Claims, Numbers

1-49 filed with the letter of 13-02-2018

Drawings, Sheets

1/22-22/22 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)).

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 20.07.2018 (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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 3, 5, 6, 30(completely); 1, 2, 4, 7-29, 31, 32(partially)
- because:
- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☒ the claims, or said claims Nos. 3, 5, 6, 30(completely); 1, 2, 4, 7-29, 31, 32(partially) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- see separate sheet**
- ☒ no international search report has been established for the said claims Nos. 3, 5, 6, 30(completely); 1, 2, 4, 7-29, 31, 32(partially)
 - ☒ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☒ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☒ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.
 - ☒ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2017/052160

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	
	No: Claims	<u>1, 2, 4, 7-28, 31(all partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1, 2, 4, 7-29, 31-49(all partially)</u>
Industrial applicability (IA)	Yes: Claims	
	No: Claims	<u>1, 2, 4, 7-29, 31-49(all partially)</u>

2. Citations and explanations (Rule 70.7):

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 III

Incomplete search

Claims 3, 6 and 30 (and also **claim 5** indirectly) refer to biological sequences identified by SEQ ID Nos. However, no sequence listings were filed. The biological sequences corresponding to the SEQ ID Nos mentioned in the claims can therefore not be searched, and no opinion can be given as to the novelty or inventive step of the corresponding subject-matter.

Claims 3, 5, 6 and 30 were not searched and no opinion is given as to the patentability of their subject-matter.

Although **claims 33-49** partially refer to **claims 3, 5, 6 and 30**, their subject-matter has been searched and examined based on the information given at tables 2 and 3 of the application as filed without a reference to the SEQ ID Nos. recited in **claims 3, 5, 6 and 30**.

Re Item V

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

1 Introduction

The present application relates to vaccination of children and young adults using a tetravalent dengue vaccine comprising a first administration of a first dose and a second administration of a second dose of the vaccine within 180 days of the first administration.

2 Cited documents

- D1** WO 2014/016360 A1 (SANOFI PASTEUR [FR]; BOUCKENOOGHE ALAIN [SG]; FORRAT REMI [FR]; LANG J) 30 January 2014
- D2** WO 2016/034629 A1 (SANOFI PASTEUR [FR]) 10 March 2016
- D3** WO 2013/188315 A1 (INVIRAGEN INC [US]) 19 December 2013
- D4** US 2015/150961 A1 (STINCHCOMB DAN T [US] ET AL) 4 June 2015

Following the filing of **new claims 33-49** it has become necessary to cite the following document for the establishment of the present opinion:

- D5** WO 2014/074912 A1 (INVIRAGEN INC [US]; US GOV HEALTH & HUMAN SERV [US]) 15 May 2014

3 **Novelty** (Art. 33(2) PCT)

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claims 1, 2, 4, 7-28, 31** is not new in the sense of Article 33(2) PCT.

3.2 The relevant passages of the cited documents should be taken from the search report.

3.3 **D1 and D2** disclose one year follow-up in Thailand of schoolchildren aged 4-11 years subcutaneously vaccinated with a tetravalent dengue vaccine (TDV) composition comprising Chimerivax™ DEN-1 , DEN-2, DEN-3 and DEN-4 (live attenuated chimeric dengue vaccines). Participants are randomly assigned 2:1 to receive three doses of dengue vaccine or a control product at Months 0, 6 ($\pm$ 15 days) and 12 ($\pm$ 15 days). The vaccine contains 2.5% human serum albumin and D-trehalose dehydrate. Other groups of patients are also mentioned in **D1**: "*Preferably a human subject according to the present invention is less than 18 years of age or less than 12 years of age. For example, a human subject according to the present invention may be 0-17 years of age, 0-1 1 years of age, 4-17 years of age, 4-1 1 years of age, 4-6 years of age, 6-8 years of age, 8-10 years of age, 2-8 years of age, 2-1 1 years of age, 2-14 years of age, 9-16 years of age, 12-17 years of age or 18-45 years of age. More preferably, a human subject according to the present invention is 4-11 years of age, 2-14 years of age or 9-16 years of age. A human subject according to the present invention may be at least 9 months old or less than 9 months old. For instance a human subject according to the present invention may be 9 months to 16 years of age, 9 months to 14 years of age, 9 months to 11 years of age or 9 months to 8 years of age*"; intramuscular, transcutaneous, subcutaneous, intranasal, oral or intradermal administrations are also cited; administration to naive and seropositive ("dengue-immune subjects") is also mentioned; patients traveling to dengue endemic regions are mentioned; administration regimen wherein the second dose is administered 3.5 months after the first dose is also mentioned ("*For instance, a vaccine composition of the present invention may be administered in a first dose, a second dose and a third dose, wherein said second dose is to be administered about six months after said first dose and wherein said third dose is to be administered about twelve months after said first dose. Alternatively, the three doses may be administered at zero months, at about three to four months (e.g. at about three-and-a-half months) and at about twelve months (i.e. a regimen wherein the second dose of the*

composition is administered at about three-and-a-half months after the first dose, and wherein the third dose of the composition is administered at about twelve months after the first dose)".

Following the objections as to lack of clarity (see **Item VIII** below), it is considered that the features of **claims 22, 24, 26 and 27** does not help distinguish the claimed subject-matter over the disclosure of **D1**.

D1 and **D2** therefore anticipate the subject-matter of **claims 1, 2, 9-14, 17-20, 22-28 and 31**.

- 3.4 **D3** and **D4** disclose immunization of seronegative human subjects with two doses of a tetravalent formulation of DENVax containing DENVax-1 (1×10^4 pfu); DENVax-22 (1×10^3 pfu); DENVax3 (1×10^4 pfu); DENVax-4 (1×10^5 pfu). The route of immunization was subcutaneous or intradermal, and the vaccinations were given 90 days apart. The vaccine induced neutralizing antibodies to all four serotypes. Compositions include chimeric dengue virus compositions where a backbone of one dengue virus can accommodate one or more of the other dengue virus components. Mixtures of these chimeric compositions can be used to generate trivalent or tetravalent formulations. the DENVax™ vaccine is composed of diluent containing Trehalose (15%) F127 (1%) and human serum albumin (0.1%) in a saline buffer to stabilize the live, attenuated vaccine formulation. The composition introduced to the subject comprises all dengue virus serotypes. In certain vaccine compositions, the ratio of DEN-1:DEN-2:DEN-3:DEN-4 can be 3:3:3:3, 4:3:4:5, 5:4:5:5, 5:4:5:5, 5:5:5:5, 5:5:5:10, 10:1:10:100 or other ratio where the ratio between 2 serotypes can be about 2 to about 100,000 fold difference (e.g. DENVax4:3:4:5™ etc.) in a single composition.

Vaccines can be administered as a prophylactic treatment to prevent infection in adults and children. A subject can be naïve or non-naïve subject with respect to exposure to dengue virus and vaccine regimens.

In addition to a 5:4:5:5 ratio for the chimeric dengue vaccines as mentioned in **D3**, **D4** also mentions a 4:4:5:5 ratio.

Following the objections as to lack of clarity (see **Item VIII** below), it is considered that the features of **claims 22, 24, 26 and 27** do not help distinguish the claimed subject-matter over the disclosure of **D1**.

D3 therefore anticipate the subject-matter of **claims 1, 2, 4, 7-12, 15-22, 25-27**.

- 3.5 **Claims 1, 2, 4, 7-28 and 31** therefore do not meet the requirements of Art. 33(2) PCT.
- 3.6 As it is not possible to assess the sequences of the of the viruses recited in **D3** and **D4**, it must be concluded that the subject-matter of **claims 33-49** (provided that it does not refer back to **claims 3, 5, 6 and 30**) is novel.
Claims 33-49 therefore meet the requirements of Art. 33(3) PCT.
- 4 **Inventive step** (Art. 33(3) PCT)
- 4.1 In the absence of a reference to specific vaccine constructs, specifying a number of plaque forming units to be used does not solve any inventive step. This applies to the subject-matter of **claims 29 and 32**, which therefore do not meet the requirements of Art 33(3) PCT concerning inventive step.
- 4.2 The selection of a specific patient population does not involve an inventive step in a generic context, as many factors such as the selection of the vaccine construct(s), the selection of the vehicles, adjuvant or stabilizers, the selection of a route of administration and of an appropriate administration regimen all participate in the efficacy and tolerability of said vaccine composition. Starting from either **D1/D2** or **D3/D4** as closest prior art, none of the claims features taken alone or in combination can be seen as imparting inventive step to the claimed subject-matter.
- 4.3 **D5** (see table 2 and 3) discloses the DEN-1, DEN-2, DEN-3 and DEN-4 viruses used in the present application. In the absence of any comparative data and i taking account of the objection under **Item VIII, paragraph 5** below, it must be concluded that the selection of the mutants of **D5** is one of the many alternative that the skilled person could choose from. Considering that **D5** offers alternative viruses selected for their prima facie improved properties, the skilled person would find obvious to combine said viruses with the methods of any **D3** or **D4** to arrive to the subject-matter of **claims 33-49** without the exercise of any inventive skills.
- 4.4 **Claims 1, 2, 4, 7-29, 31, 32-49** therefore do not meet the requirements of Art. 33(3) PCT.
- 5 **Industrial applicability** (Art. 33(4) PCT)
- 5.1 Independent **claims 1 and 28** encompass methods of therapeutic treatment practised directly onto the human body.
- 5.2 The patentability may depend upon the formulation of the claims in the Regional Phase of the procedure. 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.

Re Item VIII

Certain observations on the international application

- 1 **Claim 1** refers to "*children and young adults*". These terms do not allow to delineate beyond doubt a precise age span that would be covered by the chosen claim language. Is a patient aged 15 a child or a young adult? What is the difference between young adults aged 18 and 20? Is a patient aged 30 still considered a young adult? Where is the limit between a child and a young adult? When does an adult cease to be a "young adult"? **Claim 1** therefore does not meet the requirements of Art. 6 PCT.
- 2 **Claim 22** defines that the "*child or young adult is traveling to a dengue endemic region for the first time*". The present tense makes no sense as it is not possible to know when the child or young adult will be traveling to the dengue endemic region: after the first vaccine administration, after the second administration? Does the expression "*is traveling*" suggest a regular traveling habit? Enforcement of the claimed subject-matter appears impossible, should a patient receive the 2 vaccine administrations but finally decide not to travel to a dengue endemic region. In other terms, the intention of a patient to travel or not has no bearings with the therapeutic method and could not possibly form part of a claim subject-matter. **Claim 22** is therefore not clear.
- 3 **Claim 24** defines that the claimed therapeutic method comprises only one step of administration of the vaccine at day 0. This is in complete contradiction with the language and scope of **claim 1** which defines that the claimed method comprises one administrations at day 0 and one administration within 180 days of the first administration. The claimed subject-matter as a whole is therefore not clear.
- 4 **Claim 26** defines that "*at least 60% of the children or young adults demonstrate seropositivity to all four dengue virus serotypes after administration of the pharmaceutical composition*". Similarly, **claim 27** defines that "*at least 80% of the children or young adults demonstrate seropositivity to all four dengue virus serotypes after administration of the pharmaceutical composition*". Firstly, the claim tries to define a claimed subject-matter by reference to a result to be achieved without mentioning the features necessary to obtain this result. It is not known how this result could be

achieved over the entire claim scope. The claims therefore do not meet the requirements of Art. 5 and 6 PCT. Secondly, as not all preceding claims refer to the use of a tetravalent vaccines, it is not understood how the claimed result could possibly be achieved over the entire claim scope. For this reason also the claims do not meet the requirements of Art 5 and 6 PCT. Thirdly, it is not understood how in a method of treatment of one patient a reference can be made to statistical analysis ("60% [or 80%] of children or young adults"). The claims are therefore not clear for this reason too.

- 5 The language of **claims 33-49** ("*comprise*") does not exclude the presence of other mutations, insertions, deletions or substitutions into the sequences of the dengue viruses and therefore does not place any restriction as to the structure and as way of consequence to the function (i.e. immunogenic properties) of the virus.

IN THE PATENT COOPERATION TREATY (IPEA/EP)

International Application No. PCT/IB2017/052160	International Filing Date 13 April 2017(13/04/2017)	Earliest Priority Date 13 April 2016(13/04/2016)
Title of Invention COMPOSITIONS AND METHODS OF VACCINATION AGAINST DENGUE VIRUS IN CHILDREN AND YOUNG ADULTS		
Applicant TAKEDA VACCINES, INC.		
Attorney Docket No. 478484.265		

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European Patent Office
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GERMANY

Payment of Examination Fee, Request for Examination, Article 34 Amendments

Enclosed please find the Request for Demand and Fee Calculation Sheet for the above-referenced International Application.

The Applicant respectfully requests that the following amendments and remarks be added to the file of the above-identified International Application.

Please amend the claims by substituting the enclosed replacement pages numbered 71 to 80 for original pages 71 to 76 in International application. The substitute pages set out amendments made to the claims as follows:

Claims 1 to 32 remain unchanged. Claims 33 to 49 are presented in the substituted pages.

(i) Basis for the amendment: Basis for these claim amendments can be found throughout the specification and at least at paragraphs [00017], [00018], [00022], [00056]-[00061], [00063]-[00069], [00076], [00081], [000110], [000112], [000113], [000118]-[000119], [000125], [000126], [000137], [000155], [000156], [000162], [000163], [000167]-

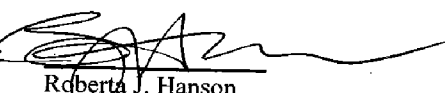
[000169], [000173], [000175], [000197]-[000216]; Tables 2-4; and the Examples of the application as originally filed.

This communication is being filed within 22-Months from the earliest priority date of 13 April 2016. Therefore, this response is timely filed and consideration of the amendments presented herein is respectfully requested.

No additional fees are deemed due. If additional fees are deemed due; the undersigned hereby authorizes the European Patent Office to charge any deficit for this submission or credit any overpayment for this response and any previous submission to EPO Deposit Account No. 28301277 and to please notify us of the same.

No new matter has been added. An annotated version of the claims followed by a clean version of the claims is provided hereinafter. The Applicant respectfully believes that this paper fulfills the requirements to indicate the basis of the proposed claim amendments to the application as filed and requests that the Article 34 Amendments be considered.

Respectfully submitted,

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Remarks/Arguments

The Applicant respectfully submits these proposed claim amendments in order to obtain a Preliminary Examination Report that includes the searching of new claims 33 to 49, in addition to, claims 1 to 32.

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What is claimed:

1. A method for treating children or young adults against dengue virus infection comprising: administering to the child or young adult, a pharmaceutical composition comprising, at least one of a live, attenuated dengue virus and a dengue-dengue chimera, wherein administering the pharmaceutical composition comprises administering a first dose of the pharmaceutical composition on day 0 and at least a second dose of the same or different pharmaceutical composition against dengue virus within 180 days of the first administration, wherein the composition induces an immune response to dengue virus in the child or young adult.
2. The method according to claim 1, wherein the pharmaceutical composition comprises all four dengue virus serotypes, a tetravalent formulation, and the pharmaceutical composition induces an immune response in the child or young adult to all four dengue virus serotypes.
3. The method according to claims 1 or 2, wherein the pharmaceutical composition comprises at least one of the following:
 - a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-2 virus serotype represented by SEQ ID NOs: 9 (Pre-Master), 11 (MVS), 13 (WVS) or 15 (BVS);
 - a dengue-1/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-1 virus serotype, represented by SEQ ID NOs: 1 (Pre-Master), 3 (MVS), 5 (WVS) or 7 (BVS);
 - a dengue-3/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-3 virus serotype, represented by SEQ ID NOs: 17 (Pre-Master), 19 (MVS), 21 (WVS) or 23 (BVS); and
 - a dengue-4/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-4 virus serotype represented, by SEQ ID NOs: 25 (Pre-Master), 27 (MVS), 29 (WVS) or 31 (BVS).

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4. The method according to any one of claims 1-3, wherein the pharmaceutical composition comprises all four dengue virus serotypes and wherein the concentration ratio of the polynucleotide encoding the live attenuated dengue-2 virus serotype in the composition is at least one half a log plaque forming unit (PFU) lower than the log PFU of one or more of other dengue virus serotypes, and
wherein the immunogenic composition elicits a balanced immune response in a subject against all four dengue virus serotypes.
5. The method according to any of claims 1-4, further comprising one or more polypeptides encoded by the polynucleotides of claim 3.
6. The method according to claim 5, wherein the polypeptide corresponding to the modified live, attenuated dengue-2 virus serotype is represented by SEQ ID NO. 10 (Pre-Master), SEQ ID NO.12 (MVS), SEQ ID NO. 14 (WVS) or SEQ ID NO.16 (BVS);
wherein the polypeptide corresponding to the dengue-1/dengue-2 chimeric polynucleotide is represented by SEQ ID NO. 2 (Pre-Master), SEQ ID NO. 4 (MVS), SEQ ID NO. 6 (WVS) or SEQ ID NO. 8 (BVS);
wherein the polypeptide corresponding to the dengue-3/dengue-2 chimeric polynucleotide is represented by SEQ ID NO. 18 (Pre-Master), SEQ ID NO.20 (MVS), SEQ ID NO. 22 (WVS) or SEQ ID NO. 24 (BVS); and
wherein the polypeptide corresponding to the dengue-4/dengue-2 chimeric polynucleotide is represented by SEQ ID NO. 26 (Pre-Master), SEQ ID NO. 28 (MVS), SEQ ID NO. 30 (WVS) or SEQ ID NO. 32 (BVS).
7. The method according to any one of claims 1 to 6, wherein the ratio of the dengue-1/dengue-2 chimera, to the live, attenuated dengue-2 virus serotype, to the dengue-3/dengue-2 chimera, to the dengue-4/dengue-2 chimera is 4:4:5:5 plaque forming units (PFU).
8. The method according to any one of claims 1 to 5, wherein the ratio of the dengue-1/dengue-2 chimera, to the live, attenuated dengue-2 virus serotype, to the dengue-3/dengue-2 chimera, to the dengue-4/dengue-2 chimera is 5:4:5:5 PFU.

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9. The method according to any one of claims 7 or 8, administering to the child or young adult a dose on day 0 and a booster 120 days or less after the dose on day 0 and inducing an immune response to all four dengue virus serotypes in the subject.
10. The method according to claim 9, wherein two doses of the immunogenic composition are administered to the subject within 30 days, or within 30, 60, 90 or 120 days of each other.
11. The method according to any one of claims 1-10, comprising administering the pharmaceutical composition to a child or young adult from 1 year to 20 years of age.
12. The method according to any one of claims 1-11, comprising administering the pharmaceutical composition to a child or young adult from 2 years to 17 years of age.
13. The method according to any one of claims 1-12, comprising administering the pharmaceutical composition to a child or young adult from 1 year to 11 years of age.
14. The method according to any one of claims 1-13, comprising administering the pharmaceutical composition to a child or young adult from 1.5 to 9 years of age.
15. The method according to any of claims 1-6 and 9-14, wherein the pharmaceutical composition comprises a formulation comprising at least one of a dengue-1/dengue-2 chimera having a concentration from 1.0×10^3 to 5×10^5 pfu; a live, attenuated dengue-2 having a concentration from 1.0×10^3 to 5×10^5 pfu, a dengue-3/dengue-2 chimera having a concentration from 5.0×10^3 to 5×10^5 pfu and a dengue-4/dengue-2 chimera having a concentration from 1.0×10^4 to 5×10^6 pfu.
16. The method according to any one of claims 1-6 and 9-15, wherein the pharmaceutical composition comprises a tetravalent formulation comprising 2.5×10^4 pfu of a dengue-1/dengue-2 chimera, 6.3×10^3 pfu of a live, attenuated dengue-2, 3.2×10^4 pfu of a dengue-3/dengue-2 chimera and 4.0×10^5 pfu of a dengue-4/dengue-2 chimera.

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17. The method according to any of claims 1-16, comprising administering the pharmaceutical composition to the child or young adult subcutaneously, intravenously, intradermally, intradermally, transdermally, orally, via inhalation, intravaginally, topically, intranasally or rectally.
18. The method according to any one of claims 1-17, wherein the pharmaceutical composition comprises a tetravalent composition and elicits an immune response to all four dengue virus serotypes in at least 60% of the children or young adults receiving one or more doses of the immunogenic composition.
19. The method according to any one of claims 1-18, wherein the at least one of a live, attenuated dengue virus and a dengue-dengue chimera further comprises a stabilizing buffer to reduce degradation of the dengue viruses.
20. The method according to claim 20, wherein the stabilizing buffer comprises trehalose and albumin and optionally, poloxamer 407.
21. The method according to claims 20, wherein poloxamer 407 has a concentration from 0.1 to 3.0 % (w/v), trehalose has a concentration from 5.0 to 50% (w/v) and albumin has a concentration from 0.01 to 3.0% (w/v).
22. The method according to any one of claims 1-8 and 11-21, wherein the child or young adult is seronegative or naive to dengue virus prior to administration of the pharmaceutical composition.
23. The method according to any one of claims 1-8 and 11-22, wherein the child or young adult is seropositive to dengue virus prior to administration of the pharmaceutical composition.

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24. The method according to claim 23, wherein the child or young adult is seropositive and the pharmaceutical composition is administered to the seropositive child or young adult on day 0 without a follow-on booster administration.
25. The method according to claim 22, wherein the child or young adult is traveling to a dengue endemic region for the first time.
26. The method according to any of claims 1-25, wherein at least 60% of the children or young adults demonstrate seropositivity to all four dengue virus serotypes after administration of the pharmaceutical composition.
27. The method according to any of claims 1-26, wherein at least 80% of the children or young adults demonstrate seropositivity to all four dengue virus serotypes after administration of the pharmaceutical composition.
28. A method for treating a human child of 1.5 to 11 years of age against dengue virus infections comprising: administering to the child a pharmaceutical composition comprising, at least one of a live, attenuated dengue virus and a dengue-dengue chimera, wherein administering the pharmaceutical composition comprises administering a first dose of the pharmaceutical composition on day 0 and at least a second dose of the pharmaceutical composition within 180 days of the first dose administration, wherein the composition induces an immune response to dengue virus in the human child.
29. The method according to claim 28, wherein the pharmaceutical composition comprises a formulation comprising at least one of a dengue-1/dengue-2 chimera having a concentration from 1.0×10^3 to 5×10^5 pfu; a live, attenuated dengue-2 having a concentration from 1.0×10^3 to 5×10^5 pfu, a dengue-3/dengue-2 chimera having a concentration from 5.0×10^3 to 5×10^5 pfu and a dengue-4/dengue-2 chimera having a concentration from 1.0×10^4 to 5×10^6 pfu.
30. The method according to claims 28 or 29, wherein the pharmaceutical composition comprises at least one of the following:

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a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-2 virus serotype represented by SEQ ID NOs: 9 (Pre-Master), 11 (MVS), 13 (WVS) or 15 (BVS);

a dengue-1/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-1 virus serotype, represented by SEQ ID NOs: 1 (Pre-Master), 3 (MVS), 5 (WVS) or 7 (BVS);

a dengue-3/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-3 virus serotype, represented by SEQ ID NOs: 17 (Pre-Master), 19 (MVS), 21 (WVS) or 23 (BVS); and

a dengue-4/dengue-2 chimeric polynucleotide comprising a nucleic acid sequence encoding nonstructural proteins from the modified live, attenuated dengue-2 virus serotype and structural proteins from a dengue-4 virus serotype represented, by SEQ ID NOs: 25 (Pre-Master), 27 (MVS), 29 (WVS) or 31 (BVS).

31. The method according to any one of claims 28-30, wherein the children are 2 to 9 years of age.

32. The method according to any one of claims 28-31, wherein the pharmaceutical composition comprises a tetravalent formulation comprising 2.0×10^4 pfu of a dengue-1/dengue-2 chimera, 5.0×10^3 pfu of a live, attenuated dengue-2, 1.0×10^5 pfu of a dengue-3/dengue-2 chimera and 3.0×10^5 pfu of a dengue-4/dengue-2 chimera and a pharmaceutically acceptable excipient.

33. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-1/dengue-2 chimeric virus polypeptide comprising at least one mutation leading to a substitution of:

an adenine to cytosine mutation at position 3823, wherein amino acid position 1243 is a leucine instead of an isoleucine; and

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an adenine to thymine mutation at position 4407, wherein amino acid position 1437 is an aspartic acid instead of a glutamic acid.

34. The method according to claim 33, wherein the nucleic acid sequence further comprises at least one mutation leading to a substitution of:

an adenine to guanine mutation at position 7311, wherein amino acid position 2405 is a proline;

a guanine to cytosine substitution at position 2384, wherein amino acid 763 is a alanine instead of a glycine; and

a cytosine to thymine substitution at position 7148, wherein amino acid position 2351 is an isoleucine instead of a threonine.

35. The method according to any one of claims 33 and 34, wherein the nucleic acid sequence further comprises:

an adenine to guanine mutation at position 7311, wherein amino acid position 2405 is a proline;

a guanine to cytosine substitution at position 2384, wherein amino acid 763 is a alanine instead of a glycine; and

a cytosine to thymine substitution at position 7148, wherein amino acid position 2351 is an isoleucine instead of a threonine.

36. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polypeptide encoded by the nucleic acid sequence according to any one of claims 33-35.

37. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polynucleotide comprising a nucleic acid sequence encoding a modified live, attenuated dengue-2 virus polypeptide comprising at least one mutation leading to a substitution of:

an adenine to guanine mutation at position 592 wherein amino acid position 166 is a glutamic acid instead of a lysine; and

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an adenine to guanine mutation at position 8803 wherein amino acid position 2903 is a valine instead of an isoleucine.

38. The method according to claim 37, wherein the nucleic acid sequence further comprises at least one mutation leading to a substitution of:

a guanine to cytosine substitution at position 6481 wherein amino acid 2129 is a proline instead of an alanine; and

a cytosine to thymine substitution at position 7156 wherein amino acid position 2354 is a phenylalanine instead of a leucine.

39. The method according to any one of claims 37 and 38, wherein the nucleic acid sequence further comprises:

a guanine to cytosine substitution at position 6481 wherein amino acid 2129 is a proline instead of an alanine; and

a cytosine to thymine substitution at position 7156 wherein amino acid position 2354 is a phenylalanine instead of a leucine.

40. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polypeptide encoded by the nucleic acid sequence according to any one of claims 37-39.

41. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-3/dengue-2 chimeric virus polypeptide comprising at least one mutation leading to a substitution of:

an adenine to thymine mutation at position 1603, wherein amino acid position 503 is a serine instead of a threonine; and

an adenine to guanine mutation at position 7620, wherein amino acid position 2508 is an alanine.

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42. The method according to claim 41, wherein the nucleic acid sequence further comprises a guanine to adenine substitution at position 6436, wherein amino acid 2114 is an asparagine instead of an aspartic acid.
43. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polypeptide encoded by the nucleic acid sequence according to any one of claims 41-42.
44. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-4/dengue-2 chimeric virus polypeptide comprising at least one mutation leading to a substitution of:
- an adenine to thymine mutation at position 225, wherein amino acid position 43 is a proline;
 - an adenine to guanine mutation at position 3674, wherein amino acid position 1193 is a glycine instead of an aspartic acid;
 - a cytosine to thymine mutation at position 5391, wherein amino acid position 1765 is an aspartic acid;
 - an cytosine to thymine mutation at position 6437, wherein amino acid position 2114 is a valine instead of an alanine;
 - a thymine to cytosine mutation at position 7026, wherein amino acid position 2310 is an alanine; and
 - a adenine to cytosine mutation at position 9750, wherein amino acid position 3218 is a proline.
45. The method according to claim 44, wherein the nucleic acid sequence further comprises at least one mutation leading to a substitution of:
- an adenine to guanine mutation at position 3773, wherein amino acid position 1193 is a glycine instead of an aspartic acid; and
 - a cytosine to thymine to substitution at position 7538, wherein amino acid 2481 is a phenylalanine instead of a serine.

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46. The method according to any one of claims 44 and 45, wherein the nucleic acid sequence further comprises:

an adenine to guanine mutation at position 3773, wherein amino acid position 1193 is a glycine instead of an aspartic acid; and

a cytosine to thymine to substitution at position 7538, wherein amino acid 2481 is a phenylalanine instead of a serine.

47. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises a polypeptide encoded by the nucleic acid sequence according to any one of claims 44-46.

48. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises at least one of the following:

a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-1/dengue-2 chimeric virus polypeptide according to any one of claims 33-35;

a polynucleotide comprising a nucleic acid sequence encoding a modified live, attenuated dengue-2 virus polypeptide according to any one of claims 37-39;

a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-3/dengue-2 chimeric virus polypeptide according to any one of claims 41-42; and

a polynucleotide comprising a nucleic acid sequence encoding a live, attenuated dengue-4/dengue-2 chimeric virus polypeptide according to any one of claims 44-46.

49. The method according to any one of claims 1-27 and 28-31, wherein the pharmaceutical composition comprises at least one of the following:

a polypeptide encoded by the nucleic acid sequence according to any one of claims 33-35;

a polypeptide encoded by the nucleic acid sequence according to any one of claims 37-39;

a polypeptide encoded by the nucleic acid sequence according to any one of claims 41-42;

and

a polypeptide encoded by the nucleic acid sequence according to any one of claims 44-46.