PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 26-11-2018

Applicant's or agent's file reference
P41704058PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2018/050893	06-09-2018	08-09-2017

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
DIAMYD MEDICAL AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will no 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/SE	Date of completion of this opinion	Authorized officer
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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: cover sheet

International Patent Classification (IPC)

G01N 33/564 (2006.01)
A61K 31/592 (2006.01)
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G01N 33/15 (2006.01)
G01N 33/569 (2006.01)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this 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:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 test file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions. Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 18-32

because:

☒ the said international application, or the said claims Nos. 18-32 relate to the following subject matter which does not require an international search *(specify):*

Claims 18-32 relate to a method for treatment of the human or animal body by surgery or therapy, see PCT Rule 43*bis*.1(b) and PCT Rule 67.1(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

☐ 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. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ 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 Searching 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 Searching 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

The following separate inventions were identified:

1: Claims 2-19, 20(partially), 22-34(p.) directed to a method for assessing the efficacy of an immunotherapy comprising administration of GAD, comprising comparing measurements in samples from a patient obtained at two points in time, for at least one of GADA IgG subclass distribution; GADA levels; distribution of cytokines secreted from lymphocytes; and lymphocyte proliferation in presence of GAD or CD3/CD28 beads. Furthermore, administration regimens of GAD in treatment or prevention of type 1 diabetes, comprising an assessment of efficacy according to the above methodology followed by an adjustment of dosage and/or administration route based on said assessment.

2: Claims 21, 20(p.), 22-34(p.) directed to administration regimens of GAD in treatment or prevention of type 1 diabetes comprising four administrations into a lymph node.

The present application has been considered to contain two inventions which are not linked such that they form a single general inventive concept, as required by Rule 13 PCT for the following reasons:

The single general concept of the present application is a method for treatment or prevention of type 1 diabetes by, possibly repeated, administration of GAD.

Document D4 discloses methods and formulations for the treatment of diabetes and the prevention of autoimmune (type 1) diabetes (see abstract). Herein, an immunotherapy trial using alum-formulated GAD65 is described (see [0056 and 0063]). A maximum of two additional booster injections were allowed in one study arm depending on the patient's GADA response, the criterium being that the GADA titre remained unchanged (defined as less than a doubling of titre prior to receipt of the first dose) at week 8 (see [0058-59]).

Thus, the single general concept is known and cannot be considered as a single general inventive concept in the sense of Rule 13.1 PCT. .../...

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. IV

No other features can be distinguished which can be considered as the same or corresponding special technical features in the sense of Rule 13.2 PCT.

Thus, the application lacks 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**

1. Statement

Novelty (N)	Claims	3-6,9-11,13-16,(19-21)*	YES
	Claims	2,7-8,12,17,(18,22-32)*,33-34	NO
Inventive step (IS)	Claims		YES
	Claims	2-17,(18-32)*,33-34	NO
Industrial applicability (IA)	Claims	2-17,(18-32)*,33-34	YES
	Claims		NO

2. Citations and explanations

Claims marked with*: (18-32)* relate to a method for treatment of the human or animal body by surgery or therapy, see PCT Rule 43*bis*.1(b) and PCT Rule 67.1(iv), see Box III.

The application comprises claims 2-34. As such, the definition of the subject matter of all claims referencing claim 1 is unclear (Article 6 PCT), see Box VIII. Consequently, it has not been possible to make an assessment for dependent claims in so far they refer to claim 1. However, claim 3 has been interpreted as if it referred to claim 2.

For further remarks on unclear claims (Article 6 PCT), see Box VIII.

Cited documents

D1: Chéramy M et al. "GAD-alum treatment in patients with type 1 diabetes and the subsequent effect on GADA IgG subclass distribution, GAD65 enzyme activity and humoral response", Clinical Immunology, 2010, 137(1):31-40
D2: US2003017509 A1
D3: Ludvigsson J et al. "Intralymphatic Injection of Autoantigen in Type 1 Diabetes", N Engl J Med, 2017, 376(7):697-699 *publ. 20170216*
D4: US2005250691 A1
D5: WO2015187087 A2

The present invention provides biomarkers and administration regimens useful in the treatment and/or prevention of type 1 diabetes.

Inventive step

Claims 2-12,17,22-32, D1

Document D1 describes a study analysing the humoral effects of a GAD-based immunotherapy in man, wherein GAD was administered subcutaneously. It had previously been shown that the GAD-alum treatment induced GADA levels in parallel to preservation of insulin secretion (i.e. a positive treatment outcome, see abstract).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

Blood samples were collected before the first injection (day 0) and 1,3,9,15,21 and 30 months post injection (compared to a "first blood…sample" and "a second blood…sample… later point in time", claim 2, see D1 p. 33). IgG1, IgG2, IgG3 and IgG4 subclasses to GADA were measured and relative frequencies calculated (see p. 36, left column, last paragraph; compared to "measuring…GADA IgG subclass distribution", claim 2).

A relative increase of IgG3 and IgG4 as well as a relative decrease of IgG1 were shown at 3 months after treatment compared to baseline (see fig. 1 and p. 36, right column, first paragraph; compared to "increased relative amount of IgG3, IgG4… or decreased relative amount of IgG1... as measured in the second sample as compared to as measured in the first sample", claim 2). This treatment-induced change at the humoral level, especially the increase in IgG4, was indicative of induction of a protective Th2 deviation in the immune response (see abstract and p. 38, left column, first paragraph). Furthermore, earlier suggestions that the protective effect of antigen-based immunotherapies relies on skewing the immune response to a Th2 associated phenotype are presented (see p. 32, left column, third paragraph). It is therefore considered implicit from D1 that a relative increase of IgG3 and/or IgG4 as well as a relative decrease of IgG1 at 3 months after treatment compared to baseline is indicative of an effective immunotherapy.

The invention according to claim 2 differs from what is known from D1 by being an explicit method for assessing the efficacy of a GAD-based immunotherapy while D1 is a study describing the humoral effects of a GAD-based immunotherapy.

Due to this feature, a practical application of the results described in D1, i.e. a method for assessing the efficacy of a GAD-based immunotherapy, is achieved.

Consequently, with the background of D1, the skilled person is posed with the problem to provide a practical application of the disclosed results. The skilled person in the field of immunology is well aware that analysis of the Th1/Th2 profile of a subject will provide information regarding the risk for developing clinical symptoms of diabetes as well as determining progression of the autoimmune response and the effect of therapies (see D2, [0010]).

The skilled person having knowledge of D1 and posed with the above problem would realise that the specified change of GADA IgG subclass distribution over time, as a measure of a protective Th2 deviation of the immune response, can be used in a method for determining the efficacy of a GAD-based immunotherapy. Thus, the skilled person would arrive at the method according to claim 2.

Therefore, the subject matter of claim 2 is considered to be obvious to a person skilled in the art. Accordingly, the invention according to claim 2 does not involve an inventive step (Article 33(3) PCT).

Using the same reasoning as for claim 2, the subject matter of claims 4-6 and 9-11 does not involve an inventive step (Article 33(3) PCT).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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The immunotherapy evaluation of D1 describes increasing GADA-levels in parallel to preservation of insulin secretion as well as referring to enhanced GADA levels at the clinically effective dosage (see abstract and p. 32, left column, last paragraph to right column, first paragraph; compared to "increased GADA levels…are indicative of an effective immunotherapy", claim 12). Thus, using a similar reasoning as for claim 2, the invention according to claim 12 lacks an inventive step (Article 33(3) PCT). Furthermore, it is considered obvious to the skilled person to use both GADA levels and subclass distribution to assess the efficacy of a GAD-based immunotherapy. No unexpected effect has been shown to be present. Accordingly, the invention according to claim 3 lacks an inventive step (Article 33(3) PCT).

The subject matter of claims 7-8, 17 and 22-32 when dependent on claim 17, concerning details of the preceding immunotherapy *per se*, is not considered to contain technical features relevant for the assessment method of claim 2. Thus, using the same reasoning as for claim 2, the subject matter of claims 7-8,17 and claims 22-32 does not involve an inventive step (Article 33(3) PCT).

Claim 16, D1 in combination with D2
The invention according to claim 16 differs further from what is known from D1 by using lymphocyte proliferation instead of GADA levels or subclass distribution as a measure of efficacy. The skilled person searching for alternatives to GADA for analysing the Th1/Th2 profile of a subject is also aware of document D2, which concerns methods for diagnosing and treating insulin-dependent diabetes mellitus in mammals. Herein, it is described that clinical symptoms of the disease are associated with the presence of Th1 cells specific for various pancreatic beta-cell-associated antigens and that an increase in the ratio of Th2 cells to Th1 cells for a specific pancreatic beta-cell-associated antigen is indicative of a protective effect (see [0025]). Beta-cell-associated antigens are exemplified to include GAD65 (see [0028]). Example 4 describes the analysis of proliferative T-cell responses after a GAD-based treatment in relation to the Th1/Th2 profile, concluding that GAD65 administration markedly reduces proliferative T-cell responses, thereby effectively inhibiting the autoimmune cascade causing the destruction of pancreatic beta-islet cells (see [0058-59]).

As is it known that type 1 diabetes is caused by a loss in tolerance and autoreactive T-cells and given that D2 describes reduced T-cell proliferation following GAD-based treatment, the skilled person would also arrive at the method according to claim 16. Thus, the invention according to claim 16 lacks an inventive step in relation to D1 in combination with D2 (Article 33(3) PCT).

Claims 7-8 and 13-15, D1 in combination with D3
The invention according to claims 7-8 (in respect of its technical content, even though not considered to be limiting features, see reasoning above) and 13-15 further differs from D1 in that the immunotherapy comprises daily administration of vitamin D and intralymphatic injections of GAD (claims 7-8), as well as measuring distribution of cytokines instead of GADA levels or subclass distribution to assess the efficacy of immunotherapy (claims 13-15). .../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

The skilled person searching for alternatives to GADA for analysing the Th1/Th2 profile of a subject is also aware of document D3, describing the results of an immunotherapy trial using intralymphatic injections of GAD for treatment of type 1 diabetes (DIAGNODE-1, NCT02352974). The trial comprised daily administration of vitamin D followed by intralymphatic injections of GAD at 1, 2 and three months after start of vitamin D treatment, which itself lasted for 4 months (see p. 697, left column, last paragraph; compared to "daily administration of vitamin D" and "intralymphatic injection of GAD at days 30, 60 and 90", claim 7 as well as "administration of vitamin D commencing at day 1 extends for 3 months or more", claim 8).

The treatment was considered effective in all patients, measured as associated with preservation of residual beta-cell function (see p. 697, right column, last sentence to p. 698, left column, first paragraph). Immunological markers showed a stepwise increase of Th2 markers such as IL-13 and IL-5 after each GAD injection (compared to "increased relative amount of IL-13 and/or IL-5", claim 13) as well as a decrease in Th1 markers such as IFNγ and TNFα (compared to "increased amount of IL-13 relative to the amount of IFNγ", claim 14, and "decreased relative amount of IFNγ and/or TNFα", claim 15; see p. 697, right column, second paragraph).

The skilled person would realise that also the results in D3 are applicable in a method for assessing the efficacy of immunotherapy as well as applicable in a GAD-based immunotherapy per se. Consequently, the skilled person would arrive at the method according to claims 7-8 and 13-15. Thus, according to the reasoning for claim 2, the invention according to claims 7-8 and 13-15 lacks an inventive step in relation to D1 in combination with D3 (Article 33(3) PCT).

A similar reasoning for claims 7-8 and 13-15 can be made from D1 in combination with D5 (for a description of D5, see below).

Novelty

Claims 2, 7-8,12, 17-18, 22-32, D4
In one embodiment, the application describes a method for treatment or prevention of type 1 diabetes by immunotherapy comprising 1) administration of GAD, 2) assessing the efficacy of the immunotherapy by measuring GADA levels at two points in time wherein increased GADA levels at the later point in time are indicative on an effective immunotherapy, 3) adjusting the dosage and/or administration route of GAD based on said assessment.

Document D4 regards methods and formulations for the treatment of diabetes and the prevention of autoimmune (type 1) diabetes (see abstract). Herein, an immunotherapy trial using alum-formulated GAD65 is described (corresponding to "administration of GAD", claim 18; see [0056 and 0063]). .../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

A maximum of two additional booster injections were allowed in one study arm depending on the patient's GADA response, the criterium being that the GADA titre remained unchanged (defined as less than a doubling of titre prior to receipt of the first dose) at week 8 (corresponding to "adjusting the dosage… on said assessment", claim 18; see [0058-59]). It is considered implicit for the skilled person that unchanged GADA levels as a criterium for extended immunotherapy means that increased GADA levels indicate an effective immunotherapy (see [0058], corresponding to "measuring GADA levels in a first… and a second…sample…comparing...measurements wherein...increased GADA levels… is indicative of an effective immunotherapy", claims 2, 12, 18 and 32).

Consequently, the subject matter of claim 18 is previously known from document D4 and therefore lacks novelty (Article 33(2) PCT). Accordingly, also claims 2, 12 and 32 lack novelty in relation to D4.

Furthermore, the subject matter of claims 7-8,17 and 22-32 when dependent on claim 17, concerning details of the preceding immunotherapy *per se*, is not considered to contain technical features relevant for the assessment method of claim 2. Thus, using the same reasoning as for claim 18, the subject matter of claims 7-8,17 and claims 22-32 lack novelty in relation to D4 (Article 33(2) PCT).

Also, the subject matter of claims 4-6 are considered detailed executions obvious to the skilled person in relation to D4 and therefore lack an inventive step in relation to D4 (Article 33(3) PCT).

Inventive step

Claims 19-20, 22-31, D4 in combination with D5
The invention according to claim 19 differs from what is known from D4 in that the adjustment of dosage includes a further administration by injection into a lymph node. The skilled person searching for alternative treatment regimens using GAD is also aware of document D5, describing a treatment regimen comprising administration of a beta cell autoantigen. The beta cell autoantigen is exemplified as GAD and the administration route intralymphatic injection into a lymph node, the most preferred administration protocol being 4 administrations at least 30 days apart (see claims 2, 15, 17 and example 2).

The skilled person with knowledge of D4 and D5 would realise that intralymphatic injections is an alternative administration route for GAD-based immunotherapy of type 1 diabetes. Thus, the skilled person would arrive at a method comprising a further administration of GAD directly into a lymph node and thus claim 19 lacks an inventive step in relation to D4 in combination with D5 (Article 33(3) PCT).

The invention according to claim 20 differs from what is known from D4 in comprising 1) administration of vitamin D commencing at day 1 and continuing for 3 to 6 months, 2) three administration of GAD into a lymph node at days 30, 60 and 90, 3) an adjustment of dosage and/or administration route including a fourth administration of GAD at a time between 12 and 18 months after day 1. .../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

The GAD-based intralymphatic immunotherapy trial DIAGNODE disclosed as example 2 in D5, from which the results have been published in D3, comprised daily vitamin D administration for four months and intralymphatic injections of GAD at days 30, 60 and 90. Adjusting the DIAGNODE administration regimen to comprise a fourth intralymphatic injection of GAD at a time between 12 and 18 months after day 1, such as at the planned visit 6 (see D5, p 57) is one option the skilled person would consider when searching for alternative treatment regimens using GAD,since no unexpected technical effect has been shown in the application regarding the time of a fourth administration compared to what is achieved in D5.

The skilled person with knowledge of D4 and D5 would realise that intralymphatic injections in combination with vitamin D administration according to example 2 of D5, supplemented with a fourth intralymphatic injection of GAD at a time between 12 and 18 months after day 1, is a suitable administration route and dosage regimen for GAD-based immunotherapy of type 1 diabetes.

Accordingly, the subject matter of claim 20 lacks an inventive step in relation to D4 in combination with D5 (Article 33(3) PCT).

Furthermore, the subject matter of claims 22-31 when dependent of claim 18 lacks inventive step in relation to D4 in combination with D5, using essentially the same reasoning as for D5 alone, see below (Article 33(3) PCT).

Claims 21-27, 29-32 D5
In one embodiment, the application describes a method for treatment or prevention of type 1 diabetes by immunotherapy comprising 1) administration of vitamin D commencing at day 1 and continuing for 3 to 6 months, 2) three administration of GAD into a lymph node at days 30, 60 and 90, 3) a fourth administration of GAD at a time between 12 and 18 months after day 1.

Document D5 relates to the prevention and/or treatment of type 1 diabetes by immunotherapy. D5 describes a treatment regimen comprising vitamin D administration at 7000-70 000 IU/week commencing 7-90 days before administration of the beta cell autoantigen and lasting 3-48 months (see claims 5-6). The beta cell autoantigen is exemplified as GAD-alum and the administration route intralymphatic injection into a lymph node, the most preferred administration protocol being 4 administrations at least 30 days apart (see claims 2, 15, 17 and example 2).

The invention according to claim 21 differs from what is known from D5 in that a specified fourth administration of GAD is performed at a time between 12 and 18 months after day 1.

No other technical effect has been shown in the application regarding the time of a fourth or further administration compared to what is achieved in D5. Furthermore, both examples of the application concern the DIAGNODE trial (NCT02352974), which is presented as example 2 in D5.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Consequently, with the background of D5, the skilled person is posed with the problem to provide an alternative point in time for the fourth administration within the GAD-based intralymphatic immunotherapy regimen.

The GAD-based intralymphatic immunotherapy trial DIAGNODE disclosed as example 2 in D5, from which the results have been published in D3, comprised daily vitamin D administration for four months and intralymphatic injections of GAD-alum at days 30, 60 and 90. Furthermore, follow-up visits were scheduled at 15 and 30 months past the first injection of GAD (i.e. 16 and 31 months past “day 1” of vitamin administration; see D5, p. 57).

Adjusting the DIAGNODE administration regimen to comprise a fourth intralymphatic injection of GAD at a time between 12 and 18 months after day 1, such as at the planned visit 6 (see D5, p 57) is one option the skilled person would consider when tasked with the problem to provide an alternative administration regimen.

The skilled person with knowledge of D5 and tasked with the above problem would adjust the treatment regimen to comprise a fourth intralymphatic injection of GAD at a time between 12 and 18 months after day 1 and thereby arrive at the treatment method according to claim 21.

Therefore, the subject matter of claim 21 is considered to be obvious to a person skilled in the art in relation to document D5. Accordingly, the invention according to claim 21 does not involve an inventive step (Article 33(3) PCT).

Similarly, the use of GAD-alum according to claim 32 when dependent on claim 21 lacks inventive step in relation to D5. Furthermore, claims 29-31 concerning vitamin D administration are considered detailed executions obvious to the skilled person in relation to the above reasoning.

HbA1c and required insulin dose are known markers of diabetes progression and are also specified as efficacy variables in example 2 of D5 (see p. 57 and p. 58 line 30 to p. 59 line 8). It is considered obvious to the skilled person to evaluate the efficacy of an ongoing treatment and adjust the treatment regimen accordingly. Since no unexpected technical effect has been shown in relation to the fourth administration of GAD, it is considered obvious to the skilled person to perform said administration if the desired efficacy has not been obtained thus far. Thus, the skilled person would arrive at the method according to claim 22. Accordingly, the invention according to claim 22 does not involve an inventive step (Article 33(3) PCT).

No unexpected technical effect has been shown in relation to further administration of GAD and consequently further administration of GAD to reach the desired outcome is considered obvious for the skilled person. Thus, using essentially the same reasoning as for claim 21, the invention according to claim 23 is considered to lack an inventive step in relation to D5 (Article 33(3) PCT).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Using essentially the same reasoning as for claim 22, the invention according to claims 24 and 25 is not considered to involve an inventive step (Article 33(3) PCT).

The efficacy variables in example 2 of D5 include increased ratio of IL-5, IL-10 and IL-13 in comparison with IFNγ, TNFα, IL-1 beta and IL-17 (see p.57 and p. 58 line 30 to p. 59 line 8). Hence, using the same reasoning as for claim 22, the invention according to claims 26-27 does not involve an inventive step (Article 33(3) PCT).

Claim 28, D5 in combination with D1
The skilled person wanting to evaluate the efficacy of a GAD-based immunotherapy is well aware of GADA and their role in type 1 diabetes.

The skilled person is also aware of D1, a study analysing the humoral effects of a GAD-based immunotherapy in man. It is considered implicit from D1 that a relative increase of IgG3 and/or IgG4 as well as a relative decrease of IgG1 at 3 months after treatment compared to baseline is indicative of an effective immunotherapy (see the above reasoning for claim 2). Thus, the skilled person would realize that a change in ratio of IgG1/IgG4 in the population of GAD specific antibodies over time is a suitable efficacy variable to use when determining the need of a further administration of GAD. Consequently, the skilled person would arrive at the method according to claim 28. Hence, using a similar reasoning as for claim 22, the invention according to claims 28 does not involve an inventive step (Article 33(3) PCT).

Novelty

Claims 33 and 34
Patentability can be dependent upon the wording of these claims. Some countries do not recognise as patentable claims to the use of a compound in medical treatment (swiss-type claims), but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Note that the “method for treatment” in both claims 33 and 34 is not limited to a method referred to in Rule 67.1 (iv).

In this case, novelty and inventive step of claim 34 has been assessed on the basis of a claim directed to the use of GAD in the manufacture of a pharmaceutical composition *suitable* for use in the method according to claim 2.

Since pharmaceutical compositions comprising GAD are known in the prior art (see D1-D5), the subject matter of claim 34 lacks novelty (Article 33(2) PCT).

As the method for treatment in claim 33 is not limited to a method referred to in Rule 67.1 (iv), claim 33 is, in its broadest sense, directed to GAD *suitable* for use in the method according to claim 2.

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Therefore, since GAD is known in the prior art and is considered to be suitable for use in the method according to claim 2, also the subject matter of claim 33 lacks novelty in relation to D1-D5 (Article 33(2) PCT).

The technical content of claim 33, when referring to claims 18 or 21, is in accordance with the technical content of these claims. Therefore, the same opinion is valid.

Summary

The subject matter of claims 2, 7-8,12, 17-18 and 22-34 lacks novelty and an inventive step. The subject matter of claims 3-6,9-11, 13-16 and 19-21 is novel, but is not considered to involve an inventive step. The subject matter of all the claims is industrially applicable.

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:

The application comprises claims 2-34. As such, the definition of the subject matter of all claims referencing claim 1 is unclear (Article 6 PCT). Consequently, it has not been possible to make an assessment for dependent claims in so far they refer to claim 1. However, claim 3 has been interpreted as if it referred to claim 2.

The reference to claim 6 in claim 8 renders the definition of the subject matter of said claim unclear, as claim 6 does not specify administration of vitamin D (Article 6 PCT). Claim 8 and has been interpreted as if it referred to claim 7.

The reference to claim 17 in claims 19 and 20 renders the definition of the subject matter of said claims unclear, e.g. claim 17 (or 2) does not specify an adjustment of the dosage of GAD (Article 6 PCT). Claims 19 and 20 have been interpreted as if they referred to claim 18.

Claims 23 and 25-28 are unclear with regards to the expressions “30 months after day 1” in claim 23 and “at days 30,60 and 90” in claims 25-28 when referring to claims 17-19, as e.g. “day 1” is not defined in these claims (Article 6 PCT). Here, “day 1” has been interpreted as the day of the first GAD injection.

Similarly, claims 30-31 are unclear with regards to the expression “wherein vitamin D is administered” when referring to claims 17-19, as the start of vitamin D administration is not defined in these claims (Article 6 PCT). Here, the start of vitamin D administration has been interpreted as the day of the first GAD injection.

Furthermore, claims 25-28 are unclear with regards to the expressions “at least three administrations” when referring to claim 21, as this claim comprises four administrations (Article 6 PCT).

The reference to claim 7 in claim 17 renders the definition of the subject matter of said claim unclear, as claim 7 specifies intralymphatic injection of GAD (Article 6 PCT). Claim 17 has been interpreted as if it referred to claims 1-6,8-15.

Claims 22 and 24 are unclear with regards to the expression “GAD-alum” as preceding claims do not specify an alum-formulation of GAD (Article 6 PCT). In these claims, “first GAD-alum” has been interpreted as “first GAD”.