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2024, January 10
OUR REF : PNAT45301-RUP DELHI
YOUR REF : 201917004058
ATTENTION : SARAVANA RAM PRASAD V G (Deputy Controller of Patents & Designs)
EMAIL : delhi-patent@nic.in/ prasadvg.ipo@nic.in

SUBMISSION OF WRITTEN NOTE OF ARGUMENTS IN RESPECT OF 201917004058 PURSUANT TO HEARING

Dear Sir,

Re : INDIA
SANOFI
INDIAN PATENT APPLICATION NO. 201917004058
FILED ON 01 February 2019
Title : ANTIBODY FORMULATIONS
Corresponding PCT Application No. : PCT/EP2017/066803 Dated 05 July 2017
Priority Details: 62/358,404 Dated 05 July 2016 of UNITED STATES OF AMERICA
16306090.8 Dated 30 August 2016 of EUROPE

Pursuant to the official communication dated 22nd November 2023 regarding the

formal hearing scheduled on 28th December 2023 by the Learned Controller of Patents & Designs Saravana Ram Prasad V G, our submissions in the matter are as follows, for and on behalf of the applicant herein.

Claims [u/s 10(5) & 10(4)(c)]

As desired by the Controller during the Hearing and in conformity with the EP allowed claim 1, the features of claim 3 have been incorporated into claim 1 and accordingly, claim 3 has been deleted from the statement of claims.

Also, claims 4 and 8-14 have been deleted from the statement of claims and the term "about" has been deleted from the claim language.

We are submitting a **marked up copy of claims and amended claim pages,** which may please be taken on record.

Regarding previous claim 3, the recited antibody or an antigen-binding fragment thereof specifically binds to the extracellular domain of the human Burkitt lymphoma receptor (i.e., CXCR5). CXCR5 is CXC chemokine receptor that affects B cell migration and tissue localization. Anti-CXCR5 binding agents are administered to subjects for treatment of inflammatory diseases. Thus, it is known that a CXCR5 antibody binds the CXC chemokine receptor. *See* page 1 of International Publication WO 2018/007456 from which the current application entered the Indian national stage. Support for the antibody formulation of claim 1, wherein now the features of claim 3 have been incorporated, comprising an isolated antibody or an antigen-binding fragment thereof that specifically binds to the extracellular domain of human CXCR5 is further supported in Example 1. *See* at least, page 2, paragraph [0007] to page 4, paragraph [0019]; page 10, paragraph [0068]; and page 33 of WO Publication 2018/007456. Applicant further notes that previously presented claim 1 recites specific ingredients, weight ratios, and concentrations that are

supported by the exemplary formulations of the specification, as originally filed. *See* page 29, paragraph [0127] of WO Publication 2018/007456.

Inventive Step & Non-Patentability

The Notice asserts an objection of previously presented claims 1-14 for lacking an inventive step. The Notice asserts the inventive step objection in view of the following documents:

D1: International Publication WO 2013/148686 A2
D2: International Publication WO 2009/032661 A1
D3: US Publication US 2014/004106 A1

With respect to the teachings of the asserted references, the Notice asserts that D1-D3 disclose all components of the formulation of previously presented claims 1-14, with the antibody of D1 having 100% similarity and all components of the formulation previously disclosed in D1. The Notice does not specifically reference D2 and D3 and as such they are not addressed herein. Moreover, the disclosure of D3 is the same as D1.

The Notice asserts the only difference between D1 and the instant application is that the formulation recited in the instant application is stored in a plastic container rather than a glass container and the formulation recited in the instant application has a higher antibody concentration. Applicant respectfully disagrees.

Claim 1 of D1 recites:

A stable formulation comprising: a binding agent comprising at least a portion of a Fc region of an IgG4 antibody; and about 5 to about 50 mM citrate as a buffering agent; wherein the pH of the formulation is at or below both about pH 6 and the pi of the binding

agent.

In contrast, claim 1 of the '058, pending application, recites a narrower formulation and specific SEQ ID NOs. for the CXCR5 antibody. **More particularly, claim 1 recites a CXCR antibody having an HC amino acid sequence of SEQ ID NO: 33 and the LC amino acid sequence of SEQ ID NO: 32. Also, an unexpected result in the current application was that a high amount of arginine in the formulation results in a stable, Stardust-particle free formulation for 6-months.** Arginine acts as a stabilizer in the formulation. *See* pages 43-44 on International Application Publication No. WO2018/007456. **Thus, when included with the antibody formulation having SEQ ID NOs. 32 and 33 the arginine stabilizes the composition.**

D1 teaches stability of twelve prototype antibody formulations, each having 100 mg/mL of CXCR5. *See* examples 17-21 of D1. Furthermore, D1 utilized mechanical stability and freeze/thaw stability testing of the formulation, excipients, and proteins at -20°C, 5°C, 20°C, and 40°C for up to six months. The results of D1 teach that CXCR5 antibody formulations having CXCR5 concentrations of 100 mg/mL are stable for at least 6 months . *See* page 113-118, and associated tables, and Examples 17-21. *See* claim 1 and the results of the Exploratory prototype stability study, page 118, paragraph [0407] of D1 and Examples 17-21 of D1. Further, D1 teaches that the CXCR5 antibody formulation is stable for at least 5 months when stored in colorless type I glass. *See* page 49, paragraph [0228], Example 8, page 50, paragraph [0234] and associated Tables 18-20. Thus, one of skill in the art would knowledge of D1 would be taught that the integrity of the CXCR5 antibody formulation is maintained during long term storage of the CXCR5 antibody formulation in glass containers.

In contrast, while conducting a compatibility study for a Phase I clinical trial, the inventors of the current disclosure determined the presence of stardust particles in the

CXCR5 formulations stored in glass vials. This discovery resulted in the Phase I study being paused. The inventors of the current application then developed a stardust free CXCR5 formulation and method of making the same, as disclosed in the current application, for use in phase II clinical trials. More specifically, using a significant number of experimental techniques, the inventors were able to develop a new formulation and determined that CXCR5 formulation stored in plastic bottles reduce eliminated stardust particle formation, exhibited a lower polydispersity index, and the plastic container did not undergo delamination. *See* page 38, paragraphs [00158] – [00160] of the current application. It was further determined that the glass components Al, Si, B, and Ca was responsible for the Stardust particle formation. *See* page 41, paragraph [00167]. **These unexpected results lead to the development of a new robust CXCR antibody formulation not prone to aggregation or stardust particle formation.**

One of skill in the art with knowledge of D1 would believe that a CXCR5 antibody formulation could be stored in glass containers until use. However, as detailed above, the inventors of the current disclosure unexpectedly determined that long term storage of the CXCR5 formulation results in an unusable product and in turn developed a solution in a stable CXCR5 antibody formulation. To believe that one of skill in the art could arrive at the disclosure of D1 is the use of impermissible hindsight.

As discussed in the specification para [0175] : *The results of the stability study showed that a* ***high amount of arginine (200 mM) results in a stable, Stardust particle-free formulation for 6 months even if the polysorbate content was at 0.01%. It was desired to achieve even higher concentrations of mAb and to achieve a formulation that is stable for a prolonged period of time. The earlier results showed that a high concentration of arginine in a formulation (Table No. 5) and a high amount of polysorbate (FIGS. 19 and 20) were beneficial. These observations were taken into account, and a new stability study was performed using high amount of arginine and polysorbate.***

In view of the above and the unexpected superior technical effect achieved with respect to stability and non-formation of stardust particles, the obviousness and Section 3 objections may please be reviewed and withdrawn.

The applicant hopefully believes that in view of the above submissions and amendments, the Learned Controller will find this application in a good condition for allowance.

For and on behalf of the applicant herein, we would humbly pray to the Learned Controller of Patents & Designs that the applicant herein be given opportunity of being heard, before issuing any adverse decision, under Section 14 or 15 of the Act, following the Principles of Natural Justice.

Yours faithfully,

(RUPSA GUPTA)
(Regn. No.: IN/PA-1613)
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Encl.: (**UPLOADED**)

1. Amended claim pages 58 - 59
2. Marked-up copy of claims

PT/AKJ/10012024

WE CLAIM :

1. An antibody formulation suitable for subcutaneous administration to a patient, the formulation comprising:

a) 100 to 175 mg/mL of an isolated anti-CXCR5 antibody or a fragment thereof that specifically binds to the extracellular domain of human CXCR5;

b) 10 mM citrate buffer;

c) 0.1% (w/v) surfactant;

d) 200 mM arginine; and

e) 4.5 to 9% sucrose,

wherein the pH of the formulation is pH 6, wherein the antibody is a fully human anti-CXCR5 antibody, and wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 32.

2. The antibody formulation as claimed in claim 1, wherein the antibody comprises a single chain Fv.

3. The antibody formulation as claimed in claim 1, wherein the surfactant is a polysorbate.

4. The antibody formulation as claimed in claim 3, wherein the polysorbate is polysorbate 20 or polysorbate 80.

5. An antibody formulation, comprising:

a) 175 mg/mL of a humanized IgG4 anti-CXCR5 antibody;

b) 10 mM citrate buffer;

c) 1.0 mg/mL polysorbate 80;

e) 200 mM arginine HCl; and

f) 45 mg/mL sucrose,

wherein the pH of the formulation is pH 6, wherein the humanized IgG4 anti-CXCR5 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 32.

Dated this 1st February, 2019

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WE CLAIM :

1. An antibody formulation suitable for subcutaneous administration to a patient, the formulation comprising:

a) ~~about~~ 100 to ~~about~~ 175 mg/mL of an isolated anti-CXCR5 antibody or a fragment thereof that specifically binds to the extracellular domain of human CXCR5;

b) ~~about~~ 10 mM citrate buffer;

c) ~~about~~ 0.1% (w/v) surfactant;

d) ~~about~~ 200 mM arginine; and

e) ~~about~~ 4.5 to 9% sucrose,

wherein the pH of the formulation is ~~about~~ pH 6, wherein the antibody is a fully human anti-CXCR5 antibody, and wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 32.

2. The antibody formulation as claimed in claim 1, wherein the antibody comprises a single chain Fv.

~~3. The antibody formulation as claimed in claim 1, wherein the antibody is an isolated antibody or an antigen-binding fragment thereof that specifically binds to the extracellular domain of human CXCR5.~~

~~4. The antibody formulation as claimed in claim 3, wherein the isolated antibody or the antigen-binding fragment thereof comprises the amino acid sequences of RSSKSLLHSSGKTYLY (SEQ ID NO: 58), RLSSLA (SEQ ID NO: 68), MQHLEYPYT (SEQ ID NO: 60), GFSLIDYGVN (SEQ ID NO: 61), VIWGDGTTY (SEQ ID NO: 62), and IVY (SEQ ID NO: 63).~~

~~5~~3. The antibody formulation as claimed in claim 1, wherein the surfactant is a polysorbate.

~~6~~4. The antibody formulation as claimed in claim ~~5~~3, wherein the polysorbate is polysorbate 20 or polysorbate 80.

~~7~~5. An antibody formulation, comprising:

a) ~~about~~ 175 mg/mL of a humanized IgG4 anti-CXCR5 antibody;

b) ~~about~~ 10 mM citrate buffer;

c) ~~about~~ 1.0 mg/mL polysorbate 80;

e) ~~about~~ 200 mM arginine HCl; and

f) ~~about~~ 45 mg/mL sucrose,

wherein the pH of the formulation is ~~about~~ pH 6, wherein the humanized IgG4 anti-CXCR5 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 32.

~~8. A container comprising the antibody formulation as claimed in any of claims 1-7.~~

~~9. The container as claimed in claim 8, wherein the container is a prefilled syringe, a vial, or an autoinjector.~~

~~10. A container comprising the antibody formulation as claimed in any of claims 1-7 in a lyophilized form.~~

~~11. A kit, comprising the container as claimed in claim 8 and a label or instructions for the administration and use of the antibody formulation.~~

~~12. The kit as claimed in claim 11, wherein administration is by injection.~~

~~13. The antibody formulation as claimed in any one of claims 1-7 for use in a method of diagnosis or treatment of a CXCR5 (C-X-C chemokine receptor type 5) mediated disease or disorder of the human or animal body.~~

~~14. A lyophilized form of the antibody formulation as claimed in any one of claims 1-7.~~