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Dated: May 12, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/148,839

Confirmation No.: 3159

Filed: May 6, 2016

Art Unit: 1644

For: TREATMENT OF PAROXYSMAL
NOCTURNAL HEMOGLOBINURIA
PATIENTS BY AN INHIBITOR OF
COMPLEMENT

Examiner: J. L. Rogers

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL
OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated April 4, 2017 (Paper No. 20170227), please amend the above-identified U.S. patent application as follows:

A Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

LISTING OF THE CLAIMS

1. **(Previously Presented)** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
2. **(Previously Presented)** A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
3. **(Previously Presented)** The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

REMARKS

Claims 1-3 are pending.

Interview Summary

Applicants thank the Examiner and his Supervisor for the interview held on May 1, 2017 and follow-up discussion on May 5, 2017, during which the outstanding rejections and related Rule 37 C.F.R. § 1.105 Request for Additional Information in the above-referenced application were discussed. The substance of the interview and follow-up discussion is reflected in the following remarks.

Moreover, as confirmed in the Interview Summary dated May 11, 2017, if the Examiners determine after consideration of the present response and accompanying Declaration that there was no 35 U.S.C. § 102(b) “public use” of the claimed invention, then there also was no 35 U.S.C. § 102(a) “knowledge or use” of the claimed invention.

Information Disclosure Statement

Applicants acknowledge with appreciation that the Information Disclosure Statements filed on May 6, 2016 and February 15, 2017 have been considered by the Examiner. Additionally, Applicants submit herewith a further Supplemental Information Disclosure Statement to make of record additional information for the Examiner’s consideration.

Rejection of Claim 2 Under 35 U.S.C. § 102(b)

The Examiner has rejected claim 2 as allegedly being anticipated by the following references, which the Examiner has characterized as follows:

Cited Reference	Examiner's Characterization
Hillmen <i>et al.</i> (<i>N. Engl. J. Med.</i> 2004; 350; 552-9), as evidenced by Applicant's specification as filed at page 44 and Thomas <i>et al.</i> (<i>Molecular Immunology</i> , 33 (17/18), pp. 1389-1401, 1996)	Hillmen <i>et al.</i> teaches a method for treating a human patient that suffers from PNH by administering to the patient an effective amount of eculizumab. Applicant's specification at page 44 discloses that SEQ ID NOs: 2 and 4 constitute the heavy and light chains of eculizumab. Thomas <i>et al.</i> teach the humanized h5G1.1 antibody, which retains the affinity and blocking functions of its murine counterpart.

Appel <i>et al.</i> (<i>Kidney International</i> , 70, S45-S50, 2006)	Appel <i>et al.</i> teaches that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5.
Wang (US2005/0271660)	Wang teaches that eculizumab inhibits activity of the complement system.

The Examiner acknowledges that none of the cited references specifically teaches that eculizumab comprises heavy and light chains consisting of the amino acid sequences set forth SEQ ID NO:2 and SEQ ID NO:4, respectively. However, the Examiner is of the opinion that, absent evidence to the contrary, these heavy and light chain sequences are "inherent properties" of eculizumab.

Applicants respectfully traverse the rejection. As explained in the April 4, 2017 Office Action on pages 3-4, the premise of the Examiner's inherency rejection is that eculizumab (and thus, its full length sequence) "was effectively in the public domain", as evidenced by Exhibit A (studies 41-60 from clinicaltrials.gov), Exhibit B (printout for NCT00005571), Exhibit C (clinicaltrials.gov from 6/23/2005 for NCT00098280), Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850). However, this is incorrect. Neither eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring, protein-engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application, as discussed in detail below. Accordingly, the presently claimed pharmaceutical composition comprising eculizumab (and the specific sequences thereof) was also not in the public domain prior to that time.

A. Exhibits A-C: Clinical Trials

With respect to the clinical trials cited by the Examiner in Appendices A-C, these clinical trials did not constitute "public use" of eculizumab under pre-AIA 35 U.S.C. § 102(b), as they were controlled, restricted, and subject to strict confidentiality obligations. Specifically, as discussed in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, the cited clinical trials using eculizumab were strictly controlled and governed by clinical trial protocols which included explicit confidentiality requirements. The Federal Circuit has clearly held that clinical trials performed under such confidentiality and restrictions do not constitute

“public use” within the meaning of 35 U.S.C. § 102(b). In *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.* (No. 2012-1428, Fed. Cir. May 20, 2013) the Federal Circuit considered whether a clinical trial constitutes an invalidating “public use” under 35 U.S.C. § 102(b). Sunovion, the accused infringer, asserted that its own clinical trial was an invalidating public use against Dey’s patents, because they involved the accused formulation and took place before Dey’s 102(b) critical date. The Federal Circuit concluded that the trial was not an invalidating public use of the study medication based on the following factors: the nature of the activity that occurred in public; the public access to and knowledge of the public use; and whether there was any confidentiality obligation imposed on persons who observed the use (citing *Bernhardt, L.L.C. v. Collezione Europa USA, Inc.*, 386 F.3d 1371, 1379 (Fed. Cir. 2004)). Applying this standard, the Federal Circuit reversed the district court’s grant of summary judgment to Sunovion because the clinical trial’s restrictions, instructions, and records requirements supported a conclusion ***that the trial was sufficiently controlled and restricted and therefore, not an invalidating public use.*** In addition, the Court noted that the *investigators (i.e., “the most knowledgeable persons involved in the study”)* were under express confidentiality restrictions, and neither the patients nor the doctors were aware of the claimed particulars of Sunovion’s formulation (page 10 of *Dey*). Specifically, “while it is true that participants were permitted to discuss the study with their doctors, ***they were not in a position to reveal the composition...because they were unaware of the specifics of the inventive formulations***” (page 10 of *Dey*). As argued by Dey and agreed by the Court, ***“if members of the public are not informed of, and cannot readily discern, the claimed features of the invention in the allegedly invalidating prior art, the public has not been put in possession of those features.”***

Similar to the facts in *Dey*, the trials cited in Exhibits A-C on page 3 of the Office Action were tightly controlled, restricted and governed by express confidentiality provisions, as discussed in detail in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone. Moreover, similar to the facts in *Dey*, the clinical trial protocols did not contain the specifics of the claimed invention or allow the participants to readily discern the features of the presently claimed invention, including the sequence of the antibody being administered, *i.e.*, eculizumab. Thus, in accordance with *Dey*, the cited clinical trials did not constitute “public use” of eculizumab under pre-AIA 35 U.S.C. § 102(b).

B. Exhibits D-H: Publications

With respect to the publications cited in Exhibit D (Kaplan 2002), Exhibit E (Appel *et al.* 2006), Exhibit F (Wang, US20050271660), Exhibit G (Rother, WO 2005/110481), and Exhibit H (Rother, US 2009/0028850), the Examiner is of the opinion that these publications demonstrate that "eculizumab was effectively in the public domain" prior to the effective filing date of the present application. In support of this assertion, the Examiner cites *In re Antor Media Corp* (CAFC, 2012) for the proposition that "the subject matter disclosed in a reference, whether it is a ***patent claim, other parts of a patent***, or non-patent literature, is presumed to be enabling absent evidence to the contrary (emphasis added)."

Applicants respectfully disagree with the Examiner's position. From the outset, as noted by the Court in *In re Antor Media Corp*, the question of enablement only arises if the cited reference in fact teaches each and every element of the claimed invention (page 9 of *In re Antor Media Corp*). In the present case, none of the publications cited in Exhibits D-H teach the complete structure of eculizumab, as presently claimed, including its complete sequence with a unique, non-naturally occurring, protein-engineered heavy chain. Nor do these references enable the presently claimed full biochemical structure of eculizumab, for the reasons discussed above. Exhibit D (Kaplan 2002) describes clinical studies that used eculizumab. Exhibit E (Appel *et al.* 2006) merely discloses that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5. Exhibit F (Wang, US20050271660) discloses antibody formulations suitable for nebulization using murine antibodies in the examples. Exhibit G (Rother, WO 2005/110481) and Exhibit H (Rother, US 2009/0028850, which was not published until after March 16, 2007) disclose the use of eculizumab for treating PNH patients, as well as the use of the mouse anti-C5 antibody BB5.1 in prolonging the survival of an allograft. Importantly, none of the cited references teach the sequence of eculizumab, let alone its unique, non-naturally occurring, protein-engineered full heavy chain (including the CH1-hinge-CH2-CH3 regions).

As discussed above, to anticipate a claimed invention, a reference must provide an enabling disclosure of the desired subject matter. Specifically, pursuant to M.P.E.P § 2121.1, "***mere naming or description of the subject matter is insufficient***, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*,

346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (emphasis added).” Further, a “reference contains an ‘enabling disclosure’ if the public was in possession of the claimed invention before the date of invention.” Such “*possession is effected if one of ordinary skill in the art could have combined the publication’s description of the invention with his [or her] own knowledge to make the claimed invention. In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (emphasis added).”

It is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application by virtue of the cited publications, because the *mere naming of eculizumab is insufficient to enable* the claimed sequences and *one of ordinary skill in the art could not have readily determined the sequences based on the limited disclosure in the publications and his or her own general knowledge.*

C. Conclusion

In sum, none of the cited references teach or enable the complete sequence of eculizumab, as presently claimed. Moreover, eculizumab was not in "public use" under 35 U.S.C. § 102(b) prior to the March 15, 2007 effective filing date of the present application, at least because the clinical trials cited by the Examiner were tightly controlled, restricted, governed by confidentiality obligations, and conducted according to protocols that did not disclose the claimed features of the invention (see *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*). Accordingly, it is clear that the public was not in possession of the claimed sequences of eculizumab prior to the effective filing date of the present application, and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Rejection of Claims 1-3 Under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen *et al.* (*N. Engl. J. Med.* 2004; 350; 552-9), in view of Evans *et al.* (US 6,355,245) and Wang (2005/0271660), and as evidenced by the parent specification (US Patent Application No.: 13/426,973). The Examiner asserts that Applicants’ argument that the complete structure of eculizumab was not disclosed in the art or available to the public is unpersuasive because "the preponderance of evidence indicates that the antibody was in public use" and this public

availability was "sufficient to have placed one of skill in the art in possession of applicant's currently claimed sequences of eculizumab."

Applicants respectfully traverse the rejection. As discussed above, neither eculizumab nor its complete sequence were available to the public or in "public use" prior to the March 15, 2007 effective filing date of the present application. Therefore, the Examiner's underlying premise supporting the present obviousness rejection (*i.e.*, that eculizumab was in "public use") is factually incorrect. Moreover, as acknowledged by the Examiner on page 7 of the Office Action, none of Hillmen *et al.*, Evans *et al.* or Wang teach or suggest the complete sequence of eculizumab. Clearly, the Examiner has failed even to establish a *prima facie* case of obviousness.

Accordingly, for at the least the above-discussed reasons, the pending claims are patentable and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Obviousness-Type Double Patenting

The Examiner has rejected claims 1-3 on the ground of non-statutory obviousness-type double patenting as being unpatentable over:

1. Claims 1-9 of US Patent No: 9,494,601 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
2. Claims 1-18 of US Patent No: 8,999,340 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
3. Claims 1-17 of US Patent No: 9,409,980 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
4. Claims 3-14 of US Patent No: 9,556,263 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
5. Claims 1-22 of US Patent No: 9,352,035 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
6. Claims 1-14 of US Patent No: 9,415,102 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
7. Claims 1-17 of US Patent No: 9,409,980 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
8. Claims 1-4 of US Patent No: 9,447,176 in view of Hillmen *et al.*, Evans *et al.*, and Wang;

9. Claims 1-5, 7, 9-16 of US Patent No: 9,388,235 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
10. Claims 15-17 and 58-59 of US Patent Application No: 11/127,438 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
11. Claims 1-4 of US Patent Application No: 15/243,386 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
12. Claims 1-4 of US Patent Application No: 15/243,290 in view of Hillmen *et al.*, Evans *et al.*, and Wang;
13. Claims 94 and 97-98 of US Patent Application No: 15/282,464 in view of Hillmen *et al.*, Evans *et al.*, and Wang; and
14. Claims 129-138 of US Patent Application No: 15/148,491 in view of Hillmen *et al.*, Evans *et al.*, and Wang.

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over US Patent No: 9,494,601, US Patent No: 8,999,340, US Patent No: 9,409,980, US Patent No: 9,556,263, US Patent No: 9,352,035, US Patent No: 9,415,102, US Patent No: 9,447,176, US Patent No: 9,388,235, US Patent Application No: 15/243,290, US Patent Application No: 15/282,464, and US Patent Application No: 15/148,491.

With respect to US Patent Application No: 15/243,386, Applicants note that this application lapsed on April 20, 2017 for failure to respond to the Office Action dated October 19, 2016. Accordingly, the rejection relating to the '386 application has been rendered moot.

Finally, with respect to US Patent Application No: 11/127,438, while the Examiner acknowledges that “the conflicting claims are not identical”, the Examiner asserts that “they are not patentably distinct from each other because both the current application and the ‘438 claim [application] claim eculizumab.” Applicants respectfully traverse this rejection.

The pending claims are drawn to pharmaceutical compositions comprising *eculizumab as defined by the complete heavy and light chain sequences of the antibody*. In contrast, claims 15-17 and 58-59 of the '438 application are drawn to an *aerosol composition* comprising h5G1.1, which is useful for the treatment of asthma. Importantly, the claims of the ‘438 application fail to recite any part of the sequence of eculizumab, let alone the complete heavy and light chain sequences. Nor does the specification of the ‘438 application teach, enable or in any way render

obvious the complete structure of eculizumab, as presently claimed. Moreover, as discussed above and in the attached Declaration, neither eculizumab nor its complete sequence were available to the public or in “public use” prior to the March 15, 2007 effective filing date of the present application. Accordingly, the mere naming of h5G1.1 in the claims of the ‘438 application does not render the present claims anticipated by or obvious over those of the ‘438 application.

A "nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s)" (see MPEP § 804). In view of the above, it is clear that the pending claims of the present '839 application and the pending claims of the '438 application are ***patentably distinct***. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Response to Request for Additional Information Under 37 C.F.R. § 1.105

In response to the Examiner's specific inquiries and request for additional information under 37 C.F.R. § 1.105, Applicants provide the following factual information, as well as the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone.

(1) Interrogatories A–F

As attested in the enclosed Declaration, Exhibits A through F cited by the Examiner on pages 7-9 of the Office Action reference 17 different clinical studies using eculizumab that occurred prior to March 16, 2007. Of the 17 studies, 4 are referred to as “extension” studies, which are studies that are appended to a clinical study to prolong the treatment and/or monitoring period of the same patients that participated in the initial study.

Of these 17 clinical studies, one that is described in both Exhibits D and F and entitled, “A Randomized, Third-Party-Blind, Placebo-Controlled, Pilot Study of the Effect of h5G1.1-mAb in Patients with Bullous Pemphigoid,” only enrolled one patient, and that one patient was randomized to receive placebo. Thus, no patient received eculizumab in the course of this study and the study was terminated.

For the remaining 16 clinical studies identified in Exhibits A through F, the below table includes: the full name of each study (and extension study thereof, if applicable, identified by an “E” or an “X” in the study number), the study number(s), the Exhibit(s) cited by the Examiner on pages 7-8 of the Office Action that each study was described in, and whether the study (including any extension study thereof) included a confidentiality provision (as described in further detail below).

Study Name¹	Study Number	Exhibit(s)	Explicit Confidentiality Provision
An Open-Label Study of the Effect of Eculizumab (h5G1.1-mAb) on Patients with Transfusion Dependent, Hemolytic, Paroxysmal Nocturnal Hemoglobinuria	C02-001	F	Yes
Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Haemoglobinuria Who Previously Participated in Study C02-001	E02-001		
An Open-Label Extension Study of Eculizumab in Patients with Transfusion Dependent, Haemolytic, Paroxysmal Nocturnal Hemoglobinuria Who Previously Participated in Study E02-001	X03-001		
A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients (TRIUMPH)	C04-001	A ² , F	Yes
Safety in Hemolytic PNH Patients Treated with Eculizumab: A Multi-Center Open-Label Research Design Study (SHEPHERD)	C04-002	A, C, F	Yes

¹ Although some of these studies may not have occurred in the United States and thus are not available to give rise to public use under 35 U.S.C. § 102(b), all of the trials have been included in this table (regardless of where they occurred).

² Of the studies referenced in Exhibit A, studies 41-43, 45-46, 52-54, 56-58 and 60 are all indicated as having been “received” or “started” *after* March 16, 2007, *i.e.*, the date eculizumab was first approved for commercial marketing and sale. Thus, only studies identified as numbers 44, 47-51, 55 and 59 in Exhibit A are included in this table.

Study Name¹	Study Number	Exhibit(s)	Explicit Confidentiality Provision
A Phase III, Open-Label, Extension Study of Eculizumab in Patients with Transfusion Dependent, Hemolytic Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have Participated in the TRIUMPH (C04-001), SHEPHERD (C04-002) or X03-001 Studies	E05-001	A, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Dermatomyositis Patients	C99-006	B, D ³ , F	Yes
Phase I Study of h5G1.1-mAb in Patients with Rheumatoid Arthritis	C97-001	F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis Patients Receiving Methotrexate	C99-001	D, F	Yes
A Phase IIB Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on Rheumatoid Arthritis (RA) Patients with Active Disease Despite Receiving Methotrexate or Leflunomide	C01-004	D, F	Yes
A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Effect of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy	C99-004	D, E, F	Yes
An Open Label Study of the Long-Term Safety of h5G1.1-mAb on the Reduction of Proteinuria in Patients with Idiopathic Membranous Glomerulopathy	E99-004		
Phase I Study of h5G1.1-mAb in Patients with Systemic Lupus Erythematosus	C97-002	D, F	Yes
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of the Effect of h5G1.1-mAb on Psoriatic Patients	C99-007	D, F	Yes
The Paroxysmal Nocturnal Hemoglobinuria Early Access Treatment Protocol (EMBRACE)	C06-002	F	Yes
PNH Registry	M07-001	A, F	Yes

³ Item 445382 referenced in the Examiner's question regarding the Kaplan reference (Exhibit D) does not refer to an actual study. However, to address any potential questions the Examiner has with respect to Exhibit D, the Kaplan reference has been reviewed in its entirety and the clinical studies described therein that used eculizumab have been included.

(i) The Antibody Sequences Used in the Clinical Studies

As attested in the enclosed Declaration, the antibody (eculizumab) used in each of the studies included in the above table contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4. However, the protocols used to conduct those studies did not inform either doctors or patients of the sequences.

(ii, iii) Confidentiality Provisions in the Clinical Studies

As indicated in the table above and discussed in the enclosed Declaration, in the course of conducting each of the clinical trials listed, participating physicians and others involved in the study were required to maintain Alexion's confidential and/or proprietary information in strict confidence. For example, these individuals were required to maintain the confidentiality of the clinical trial protocols themselves, as each protocol was marked "Confidential". These individuals were also bound by explicit confidentiality provisions in the protocol. As attested to in the attached Declaration of Dr. Boone, the following language from the protocol for study number C04-001, which refers to the Phase III TRIUMPH study, provides a representative example of the confidentiality requirements set forth directly within these clinical study protocols:

"THE INVESTIGATOR AND ALL EMPLOYEES AND COWORKERS INVOLVED WITH THIS STUDY SHALL NOT DISCLOSE OR USE FOR ANY PURPOSE, OTHER THAN PERFORMANCE OF THE STUDY, ANY DATA, RECORDS OR OTHER UNPUBLISHED, CONFIDENTIAL INFORMATION DISCLOSED TO THOSE INDIVIDUALS FOR THE PURPOSE OF THE STUDY. PRIOR WRITTEN AGREEMENT FROM THE SPONSOR OR ITS DESIGNEE MUST BE OBTAINED FOR THE DISCLOSURE OF ANY SAID CONFIDENTIAL INFORMATION TO OTHER PARTIES."

As another representative example, Dr. Boone cites the protocol for the study in dermatomyositis (study number C02-002), which stated:

"THIS CONFIDENTIAL INFORMATION ABOUT AN INVESTIGATIONAL DRUG IS PROVIDED FOR THE EXCLUSIVE USE OF INVESTIGATORS

OF THIS DRUG AND IS SUBJECT TO RECALL AT ANY TIME. THE INFORMATION IN THIS DOCUMENT MAY NOT BE DISCLOSED UNLESS SUCH DISCLOSURE IS REQUIRED BY FEDERAL OR STATE LAW OR REGULATIONS SUBJECT TO THE FOREGOING. THIS INFORMATION MAY BE DISCLOSED ONLY TO THOSE PERSONS INVOLVED IN THE STUDY WHO HAVE A NEED TO KNOW WITH THE OBLIGATION NOT TO FURTHER DISSEMINATE THIS INFORMATION. THESE RESTRICTIONS ON DISCLOSURE WILL APPLY EQUALLY TO ALL FUTURE ORAL OR WRITTEN INFORMATION SUPPLIED TO YOU BY ALEXION, WHICH IS DESIGNATED AS 'PRIVILEGED' OR 'CONFIDENTIAL'."

As Dr. Boone explains, all confidentiality provisions in the protocols for the studies listed in the table above were substantively identical to these representative confidentiality provisions from studies C04-001 and C02-002.

In addition, Dr. Boone attests that each clinical trial protocol required strict control over the physical drug product (eculizumab). For example, the clinical trial protocol for the TRIUMPH study described the secure storage and inventory and disposal requirements of each participating physician and study site as shown below:

"Eculizumab must be stored in a secure, limited-access storage area. . . .

Test Article Accountability...When a drug shipment is received at the site, the pharmacist at each site shall verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor. The duplicate copy should be kept in the pharmacy binder.

Each shipment of investigational drug supplies will contain an accountability log to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the investigational product. During the study, the following information must be noted in the accountability log: the identification number(s), initials of patient(s) who is dispensed investigational product, the date(s) that the investigational product is prepared and dispensed, and the initials of the pharmacist or designee who prepared the investigational product. Empty vials and vials with residual materials should be kept for inspection by the study monitor.

The study monitor will examine the inventory records during study conduct. Additionally, the inventory records must be readily available and may be subject

to regulatory authorities or an independent auditor's inspection at any time. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all remaining investigational product inventory will be reconciled and retained or destroyed according to applicable local, state, and federal regulations."

Dr. Boone also explains that all of the protocols for the studies listed in the above table included similar (if not identical) drug storage and accountability provisions, except for the PNH Registry protocol (the last entry in the table above). The PNH Registry was not a study in which eculizumab was administered to any patients; rather, it was a "non-interventional study designed to collect post-marketing pharmacovigilance and effectiveness data on patients treated with Soliris® (eculizumab)" and to "collect information on the progression of disease in the Soliris treated and untreated PNH patient population." Accordingly, the protocol for the PNH Registry did not contain drug storage or accountability provisions. The PNH Registry protocol did, however, include strict confidentiality provisions as indicated in the table above, *e.g.*, requiring all physicians to "agree to maintain the confidentiality of all information received or developed in connection with [the] protocol."

(iv) Physicians Acting at Alexion's Direction

As discussed in the enclosed Declaration, to participate in each clinical trial listed in the table above, each physician had to sign the protocol for the trial, committing to adhere to the respective clinical trial protocol's provisions. For example, the TRIUMPH study protocol, just prior to the physician's signature line, stated:

"I agree to conduct the study as outlined in the protocol entitled: "*TRIUMPH: A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients*" and in accordance with the guidelines and all applicable government regulations. I have read and understand all sections of the protocol including Section 11, Administrative Considerations."

As Dr. Boone states, all of the other protocols similarly required each physician (or investigator) to agree to conduct the study in accordance with the protocol.

(2) Interrogatory G

As attested in the enclosed Declaration, the antibody having the heavy chain described by SEQ ID NO:2 and the light chain described by SEQ ID NO:4 was first approved for commercial marketing and sale on March 16, 2007.

CONCLUSION

In view of the above amendment, arguments, and accompanying Declaration, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 217-4630.

Applicants believe no fee is required with this submission. However, should any additional fee be due, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN2.

Dated: May 12, 2017

Respectfully submitted,

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