goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol (see paragraph bridging pages 19-20 of the disclosure) and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 37-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ding et al. (US 5,474,979, cited in the IDS dated 12/27/2004).

Ding et al. disclose topical ophthalmic emulsions for treating an eye of human having KCS (dry eye disease), and a method comprising topically administering to the eye the human emulsion (see next page):

Example 1

	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

Thus, a comparison of the instantly claimed and some of the Ding et al. embodiments is presented below:

	DING et al. 1-D	instant invention	DING et al. 1-E
Cyclosporin	0.10%	0.05%	0.05%
Castor oil	1.25%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%
Pemulen	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%
NaOH	qs	qs	qs
Purified water	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6

Furthermore, the claims of Ding et al. disclose ranges for the components (e.g., claims 1-8). For example, Ding et al. discloses a pharmaceutical emulsion comprising

cyclosporin A, castor oil, Pemulen, glycerine, polysorbate 80, water in amounts sufficient to prevent crystallization of cyclosporin A for a period of up to about nine months, said pharmaceutical emulsion being suitable for topical application to ocular tissue, wherein the cyclosporin A is present in an amount between about 0.05 to and about 0.40%, by weight, the castor oil is present in an amount of between about 0.625%, by weight, and about 5.0%, by weight, the polysorbate 80 is present in an amount of about 1.0%, by weight, the Pemulen is present in an amount of about 0.05%, by weight, and the glycerine is present in an amount of about 2.2%, by weight (e.g., claims 7-8).

The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome with Examples 2, 3 and 4 without the active ingredient cyclosporin utilized to determine the toxicity of the emulsified components.

Ding et al. teach that the formulations in Examples 1-4 were applied to rabbit eyes eight times a day for seven days and were found to cause only slight to mild discomfort and slight hyperemia in the rabbit eyes. Slit lamp examination revealed no changes in the surface tissue. In addition, the cyclosporin containing castor oil emulsion, as hereinabove set forth in Examples 1A-1D, was also tested for ocular bioavailability in rabbits; and the therapeutic level of cyclosporin was found in the tissues of interest after dosage. Ding et al. go on to teach that this substantiates that cyclosporin in an ophthalmic delivery system is useful for treating dry eye.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al., e.g., Example 1E, by making any composition (and method thereof) encompassed by the ranges disclosed in Ding et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so given the guidance provided by Ding et al., i.e., the amount of castor oil in the emulsions is taught to be cyclosporin to castor oil is between 0.12 and 0.02, which, for 0.05% corresponds to 0.4% to 2.5% of castor oil (which encompasses 1.25%). See, e.g., col. 3. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because 1.25% was known to be non-irritating as shown in Example 1D, because such modifications are routinely determined and optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding optimization of ranges] and because the active ingredients, cyclosporin A and castor oil were present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)]. Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (MPEP 716.02). Furthermore, one of ordinary skill in the art would have been motivated to determine adequate daily frequency of administration in order to find suitable administration

regimes (e.g., once, twice, thrice, etc.), one of ordinary skill in the art at the time the invention was made would have had reasonable expectation of success given that the 0.1% containing cyclosporin emulsion was effective in treating KCS (see Examples).

Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In the instant case, the limitations “, [..] the blood of the human has substantially no detectable concentration of cyclosporin A”, “wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compare to an emulsion that contains only 50% as much castor oil”, ”wherein the ophthalmic emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human”, “wherein the adverse events include side effects” and “wherein the emulsion is effective in increasing tear production in the human having KCS”, it is noted that such functional effects would necessarily flow

from the compositions of Ding et al. and methods thereof which comprise administration of all the claimed components and amounts in the claimed method, as set forth above.

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue 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, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

7. Claims 37-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,474,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because Ding et al. (US 5,474,979) claims pharmaceutical emulsions comprising of cyclosporine A, castor oil, Pemulen ® (crosslinked polyacrylate stabilizer), glycerine and water as instantly claimed (see claims 6-8 of Ding et al.) for topical application comprising to ocular tissue wherein the cyclosporine A is presents in an amount of between about 0.05 to and about 0.40% by weight (which encompasses about 0.05% cyclosporin A), castor oil from about 0.625% to about 5.0% (which encompasses 1.25% of castor oil), Pemulen ® at about 0.05%, and glycerin at about 2.2%. (see, e.g., claim 8). Additionally, a different emulsifier, i.e., polysorbate 80, is

taught at about 1.0% (see also claim 8). The emulsion contains water as set forth in claims 6-8 of Ding et al. The specification of Ding et al. was used as dictionary and it was determined that the compositions were used to treat dry eye (KCS) and that the compositions encompassed Examples 1A-E, wherein 1E comprises all the components and ranges instantly claimed except for the castor oil, which is encompassed by the claimed ranges to cyclosporin to castor oil.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al. by making any compositions encompassed by the ranges taught by Ding et al. One of ordinary skill in the art would have been motivated to do so in order to create nonirritating emulsions of cyclosporin suitable for topical application to ocular tissue. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because such modifications are routinely determined and optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding optimization of ranges] and because the active ingredients, cyclosporin A and castor oil were present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)]. Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range

(MPEP 716.02). Furthermore, one of ordinary skill in the art would have been motivated to determine adequate daily frequency of administration (e.g., once, twice, thrice, etc.) in order to find suitable administration regimes, one of ordinary skill in the art at the time the invention was made would have had reasonable expectation of success given that the 0.1% containing cyclosporin emulsion was effective in treating KCS (see Examples).

Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In the instant case, the limitations “wherein the topical ophthalmic emulsion is therapeutically effective in treating KCS”, “wherein, when the topical ophthalmic emulsion is administered to an eye of a human, [..] the blood of the human has substantially no detectable concentration of cyclosporin A”, “wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compare to an emulsion that contains only 50% as much castor oil”, ”wherein the ophthalmic emulsion, when administered to the eye of a human,

demonstrates a reduction in adverse events in the human", "wherein the adverse events include side effects" and "wherein the emulsion is effective in increasing tear production in the human having KCS"; it is noted that such functional effects would necessarily flow from the compositions and methods claimed and exemplified by Ding et al. which comprise all the claimed components, amounts and methods as set forth above.

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-60 of copending Application No. 13/961,818. Although the claims at issue are not identical, they are not patentably distinct from each other because US '818 is drawn to a method which encompasses a method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water and castor oil in an amount of about 1.25% by weight.

The other claims in US '818 are also drawn to the corresponding methods.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

9. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-61 of copending Application No. 13/967,179. Although the claims at issue are not identical, they are not patentably distinct from each other because US '179 is drawn to a method comprising topically administering to the eye of the human an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight.

The other claims in US '179 are also drawn to the corresponding methods.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

10. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-61 of copending Application No. 13/967,163. Although the claims at issue are not identical, they are not patentably distinct from each other because US' 163 is drawn to an emulsion comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease. Thus, it inherently discloses a method of treating dry eye disease/increasing tear production (claim 37 of the instant application). The other claims in US '163 are also inherently drawn to the corresponding claimed methods. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)].

Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (MPEP 716.02).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

11. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-61 of copending Application No. 13/961,828. Although the claims at issue are not identical, they are not patentably distinct from each other because US' 828 is drawn to an emulsion comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease. Thus, it inherently discloses a method of treating dry eye disease/increasing tear production (claim 37 of the instant application). The other claims in US '828 are also inherently drawn to the corresponding claimed methods. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)]. Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (MPEP 716.02).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

12. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-60 of copending Application No. 13/967,189. Although the claims at issue are not identical, they are not patentably distinct from each other because US' 189 is drawn to an emulsion comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease/increasing tear production. Thus, it inherently discloses a method of treating dry eye disease (claim 37 of the instant application). The other claims in US '189 are also inherently drawn to the corresponding claimed methods. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)]. Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (MPEP 716.02).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

13. Claims 37-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37-60 of copending Application No. 13/961,808. Although the claims at issue are not identical, they are not patentably distinct from each other because US' 808 is drawn to an emulsion comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water,

and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease. Thus, it inherently discloses a method of treating dry eye disease/increasing tear production (claim 37 of the instant application). The other claims in US '808 are also inherently drawn to the corresponding claimed methods. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)]. Furthermore, to establish **unexpected results** over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (MPEP 716.02).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Statutory double patenting

14. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no

longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

15. Claims 37-60 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 37-60 of copending Application No. 13/961,835. The claims are identical too each other, i.e., claim 37 in both applications are drawn to method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in increasing tear production. The other claims in US '835 are identical to the corresponding claims in the instant invention.

This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

Conclusion

16. No claim is currently allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

MMCG 10/2013

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/967,168	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1658	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA WINE*. (4)_____.

Date of Interview: _____.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37 and 59*.

Identification of prior art discussed: *Ding et al. (US 5,474,979)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1658	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicants' representative contacted Examiner to request an in-person interview to discuss the case and also indicated that Applicants would be willing to amend the trademark Pemulen in the claims for acrylate/C10-30 alkyl acrylate cross-polymer (see attachment). This potential amendment was not deemed sufficient to make the claims allowable. During the in-person interview on 10/3/2013 the following attendees were present: Laura Wine, Debra Condino, Dr. Rhett Schiffman, Dr. Maysa Attar, and Examiner Cordero Garcia. Applicant's representatives described the backroung of dry eye disease, the process of arriving at the claimed invention and discussed: a) unexpected results, b) commercial success and c) long felt need. Further, the Ding et al. patent (US 5,474,979) was discussed with regards to its contents and relation to the claimed invention. With regards to the presented unexpected results, Examiner indicated that it would be necessary to include in a 37 CFR 1.32 declaration all the experimental conditions for the various clinical trials used in the 'unexpected results' evidence, in order to determine whether these clinical trials can be effectively used in the comparison of therapeutic effects of the cyclosporin compositions of Ding et al. with the claimed invention. Examiner also indicated that a first Office Action on the merits would be provided shortly after the interview since the proposed amendment would not obviate all rejections deemed necessary (see attached Office Action) and also briefly discussed potential statutory and non-statutory double patenting issues for the instant application. A courtesy draft of the Office Action for a related case was provided to Applicant's representatives.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S3	377	cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/04 16:09
S4	12	cyclosporin same castor same polysorbate same pemulen	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 09:54
S5	19	cyclosporin same "0.05" same castor same "1.25"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 09:59
S6	89	cyclosporin same castor same polysorbate	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 10:21
S7	4	cyclosporin same castor same polysorbate same pemulen same hydroxide	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 10:21
S8	104	"5474979"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 12:06
S9	2	"5474979".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 12:06

10/7/2013 2:09:34 PM

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S3	377	cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/04 16:09
S4	12	cyclosporin same castor same polysorbate same pemulen	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 09:54
S5	19	cyclosporin same "0.05" same castor same "1.25"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 09:59
S6	89	cyclosporin same castor same polysorbate	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 10:21
S7	4	cyclosporin same castor same polysorbate same pemulen same hydroxide	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 10:21
S8	104	"5474979"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 12:06
S9	2	"5474979".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2013/10/05 12:06

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CONFIRMATION NO. 3265

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/967,168	08/14/2013	514	1658	17618CON7B (AP)

APPLICANTS

Alllergan, Inc., Irvine, CA, Assignee (with 37 CFR 1.172 Interest);
Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, NV;
James N. Chang, Newport Beach, CA;
David F. Power, Hubert, NC;

**** CONTINUING DATA ***************************

This application is a CON of 13/961,835 08/07/2013
which is a CON of 11/897,177 08/28/2007
which is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

09/03/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /MARCELA M CORDERO GARCIA/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	24	3

ADDRESS

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599
UNITED STATES

TITLE

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

FILING FEE RECEIVED		
2360	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1	ABDULRAZIK, M. ET AL, Ocular Delivery of Cyclosporin A II. Effect of Submicron Emulsion's Surface Charge on Ocular Distribution of Topical Cyclosporin A, S.T.P. Pharma Sciences, Dec. 2001, 427-432, 11(6)	☐
	2	ACHEAMPONG, ANDREW ET AL, Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog and Human eyes, 1996, 179	☐
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Receipt date: 09/12/2013	Application Number	13967168 13967168 - GAU: 1658
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2013-08-14
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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	67	U.S. Pending Application: 13/961,818 Filed on August 07, 2013	☐
	68	U.S. Pending Application: 13/967,163 Filed on August 14, 2013	☐
	69	U.S. Pending Application: 13/961,808 Filed on August 07, 2013	☐
	70	U.S. Pending Application: 13/961,828 Filed on August 07, 2013	☐
	71	U.S. Pending Application: 13/916,835 Filed on August 07, 2013	☐
	72	U.S. Re-Examination Application: 90/009,944 Filed on August, 27, 2011	☐

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	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

EXAMINER SIGNATURE			
Examiner Signature	/Marcela Cordero Garcia/	Date Considered	10/05/2013

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	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON7-AP

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2013-09-12
Name/Print	Laura L. Wine	Registration Number	68,681

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DRAFT CLAIM AMENDMENT
U.S. Patent Application No. 13/967,168
Attorney Ref: 17618CON7B (AP)
FOR DISCUSSION PURPOSES ONLY

37. (**Currently Amended**) A method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, ~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in increasing tear production.

59. (**Currently Amended**) A method comprising:

administering an emulsion topically to the eye of a human having KCS, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water; and

wherein the emulsion is effective in increasing tear production in the human having KCS.

Interview Agenda

U.S. Patent Application Nos. 13/967,189; 13/967,179; 13/967,163; and 13/967,168 – METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Examiner Marcela Cordero Garcia – (410) 262-3037

- **Introduction**
- **Discussion of Claimed Subject Matter**
  - **Background on Dry Eye Disease**
  - **The Development and Innovation of the Claimed Formulation**
- **Presentation of Objective Evidence of Non-Obviousness**
  - **Unexpected Results**
  - **Commercial Success**
  - **Long Felt Need/Failure of Others**
- **Brief Discussion of Prior Art**
  - **Ding (U.S. Patent No. 5,474,979)**
- **Discussion of Clarifying Amendments**

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13967168	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1658

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
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US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	10/7/2013	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	10/7/2013	MMCG
STN search (attached)	10/7/2013	MMCG
also ran PALM Inventor search	10/7/2013	MMCG

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NEWS	11	FEB 22	2013 MARPAT Backfile Expansion Update
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NEWS	18	MAY 21	STN Updated to Reflect Streamlining of CAS Roles
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NEWS	20	MAY 28	STN Adds Indian Patent Full Text File - INFULL
NEWS	21	JUL 09	TULSA and TULSA2 were reloaded on July 8, 2013
NEWS	22	JUL 15	New IFIALL Database on STN Increases US Patent Retrieval Capabilities
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NEWS	24	JUL 31	New PV Cluster on STN(R) Simplifies Pharmacovigilance Alerting and Searching
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NEWS	26	AUG 15	PCTFULL documents with Chinese, Japanese, or Korean as filing language have English machine translations
NEWS	27	AUG 16	The 2013 Inventory of Existing Chemical Substances in China is Now Available on STN
NEWS	28	SEP 10	CAS Expands Coverage of Philippines Patents
NEWS	29	SEP 13	STN on the Web Enhanced with Updated Structure and BLAST Plug-ins
NEWS	30	SEP 24	Emtree Thesaurus Updated in Embase
NEWS	31	SEP 27	Application Numbers for U.S. Patents in CA/CAplus and USPATFUL/USPAT2 Enhanced with U.S. Series Code Information

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 NEWS 32  OCT 04  Impacts of U.S. Government Shutdown on STN Databases

 NEWS EXPRESS 23 MAY 2012 CURRENT WINDOWS VERSION IS V8.5.1,
              AND CURRENT DISCOVER FILE IS DATED 22 JULY 2013.

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=> (cyclosporin or cyclosporine) (10a) ("castor oil") (10a) polysorbate
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command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file biosis embase medline pubmed
'PUBMED' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       2.16       2.16

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FILE 'MEDLINE' ENTERED AT 14:16:25 ON 07 OCT 2013

=> file biosis embase medline caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       3.67       5.83

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FILE 'MEDLINE' ENTERED AT 14:16:34 ON 07 OCT 2013
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FILE 'CAPLUS' ENTERED AT 14:16:34 ON 07 OCT 2013
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=> (cyclosporin or cyclosporine) (10a) ("castor oil") (10a) polysorbate
L1 12 (CYCLOSPORIN OR CYCLOSPORINE) (10A) ("CASTOR OIL") (10A) POLYSOR
BATE

=> d ibib abs total hitseq

L1 ANSWER 1 OF 12 BIOSIS COPYRIGHT (c) 2013 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:456121 BIOSIS
DOCUMENT NUMBER: PREV200600453000
TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation.
AUTHOR(S): Yang, S. G.; Kim, D. D.; Chung, S. J.; Shim, C. K. [Reprint Author]
CORPORATE SOURCE: Seoul Natl Univ, Coll Pharm, Dept Pharmaceut, San 56-1,Shinlim Dong, Seoul 151742, South Korea
shimck@snu.ac.kr
SOURCE: International Journal of Clinical Pharmacology and Therapeutics, (MAY 2006) Vol. 44, No. 5, pp. 233-239.
ISSN: 0946-1965.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Sep 2006
Last Updated on STN: 13 Sep 2006

AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved physical stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to commercially available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 ml of water with a 1-week washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment Q. Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concentrations using a specific monoclonal radioimmunoassay. Results: The differences in bioavailability parameters (i.e., AUC(0-24h), AUC(0-infinity) and C-max) between the treatments were within the range of 80 - 125% of the reference treatment. An analysis of variance (ANOVA) revealed no significant differences ($p > 0.05$) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and Q were also within the criteria. Conclusion: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin

appears to have an advantage over the commercial soft capsules of CsA using a volatile cosolvent such as ethanol.

L1 ANSWER 2 OF 12 EMBASE COPYRIGHT (c) 2013 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006216678 EMBASE
TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation.
AUTHOR: Yang, S.G.; Kim, D.D.; Chung, S.J.; Shim, C.-K., Dr. (correspondence)
CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul 151-742, Korea, Republic of. shimck@snu.ac.kr
AUTHOR: Shim, C.-K., Dr. (correspondence)
CORPORATE SOURCE: Department of Pharmaceutics, College of Pharmacy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul 151-742, Korea, Republic of. shimck@snu.ac.kr
SOURCE: International Journal of Clinical Pharmacology and Therapeutics, (May 2006) Vol. 44, No. 5, pp. 233-239. Refs: 22
ISSN: 0946-1965 CODEN: ICTHEK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 30 May 2006
Last Updated on Embase: 6 Sep 2007

AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved physical stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to commercially available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 ml of water with a 1-week washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment C). Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concentrations using a specific monoclonal radioimmunoassay. Results: The differences in bioavailability parameters (i.e., AUC0-24h, AUC0-∞ and Cmax) between the treatments were within the range of 80-125% of the reference treatment. An analysis of variance (ANOVA) revealed no significant differences ($p > 0.05$) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and C) were also within the criteria. Conclusion: These results indicate that the

bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the commercial soft capsules of CsA using a volatile cosolvent such as ethanol. .COPYRGT. 2006 Dustri-Verlag Dr. K. Feistle.

L1 ANSWER 3 OF 12 MEDLINE ® on STN
ACCESSION NUMBER: 2006296965 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16724578
TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation.
AUTHOR: Yang S G; Kim D D; Chung S J; Shim C K
CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul, Korea.
SOURCE: International journal of clinical pharmacology and therapeutics, (2006 May) Vol. 44, No. 5, pp. 233-9. Journal code: 9423309. ISSN: 0946-1965. L-ISSN: 0946-1965.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL) (CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 27 May 2006
Last Updated on STN: 12 Dec 2006
Entered Medline: 20 Jul 2007

AB AIM: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved physical stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to commercially available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA.

VOLUNTEERS AND METHODS: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 ml of water with a 1-week washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment C). Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concentrations using a specific monoclonal radioimmunoassay.

RESULTS: The differences in bioavailability parameters (i.e., AUC(0-24h), AUC(0-infinity) and C(max)) between the treatments were within the range of 80-125% of the reference treatment. An analysis of variance (ANOVA) revealed no significant differences ($p > 0.05$) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and C) were also within the criteria.

CONCLUSION: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the commercial soft capsules of CsA using a volatile cosolvent such as ethanol.

L1 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 2013:569214 CAPLUS
DOCUMENT NUMBER: 158:545244
TITLE: Topical oil-in-water emulsion compositions for enhancing nail health comprising immunomodulator such as cyclosporine
INVENTOR(S): Walt, John G.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 115pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013052424	A2	20130411	WO 2012-US58333	20121001

W: 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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2011-61543758 P 20111005

AB The present invention is directed to compns. and methods for enhancing the health of nails and cuticles in a mammal, including humans. The compns. may be administered topically to the nail bed, nail matrix and cuticle in an amount effective to enhance nail health. The composition is also effective in strengthening and growing nails. Thus, the disclosed compns. comprised immunomodulator such as cyclosporine, antiinflammatory such as ketorolac, castor oil, surfactant, glycerin, polysorbate 80 and carbomer.

L1 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 2007:119452 CAPLUS
DOCUMENT NUMBER: 146:190563
TITLE: Pharmaceutical compositions comprising cyclosporins
INVENTOR(S): Tien, Walter L.; Graham, Richard; Chang, James N.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 4pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 20070027072 A1 20070201 US 2005-161218 20050727
US 7501393 B2 20090310
WO 2007016073 A1 20070208 WO 2006-US28788 20060725
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
US 20090131307 A1 20090521 US 2009-361335 20090128
PRIORITY APPLN. INFO.: US 2005-161218 A 20050727
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A composition is described herein comprising cyclosporin A, Polysorbate 80, a polyoxyethylene stearate, and an oil; wherein the composition is an emulsion which is ophthalmically acceptable. Methods of treating diseases or conditions using the compns., and medicaments related thereto, are also disclosed herein. Thus, a composition contains purite 100 ppm cyclosporin A 0.1, castor oil 0.5, PEG stearate 1.0, Polysorbate-80 0.5, glycerin 1.4, boric acid 0.6, CM-cellulose 0.5, and water qs to 100%.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 2007:63260 CAPLUS
DOCUMENT NUMBER: 146:149038
TITLE: Opthalmic emulsion comprising cyclosporin
INVENTOR(S): Chang, James N.; Olejnik, Orest; Firestone, Bruce A.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 24pp., Cont.-in-part of U.S. Ser. No. 181,409.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070015694	A1	20070118	US 2005-255821	20051019
US 7288520	B2	20071030		
US 20070015690	A1	20070118	US 2005-181178	20050713
US 7297679	B2	20071120		
US 20070015710	A1	20070118	US 2005-181187	20050713
US 7276476	B2	20071002		
US 20070015691	A1	20070118	US 2005-181409	20050713
US 20070015692	A1	20070118	US 2005-181428	20050713
US 7202209	B2	20070410		
US 20070015693	A1	20070118	US 2005-181509	20050713
US 20070149447	A1	20070628	US 2007-679934	20070228
US 8536134	B2	20130917		
US 20080009436	A1	20080110	US 2007-857223	20070918
US 8211855	B2	20120703		
US 20080070834	A1	20080320	US 2007-940652	20071115

US 20120270805 A1 20121025 US 2012-13536479 20120628
PRIORITY APPLN. INFO.: US 2005-181178 A2 20050713
US 2005-181187 A2 20050713
US 2005-181409 A2 20050713
US 2005-181428 A2 20050713
US 2005-181509 A2 20050713
US 2005-255821 A3 20051019
US 2007-857223 A1 20070918
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A composition is disclosed herein comprising from about 0.001% to about 0.4% cyclosporin A, castor oil, and a surfactant selected from the group consisting of alc. ethoxylated, alcs., alkyl glycosides, alkyl polyglycosides, alkylphenol ethoxylates, amine oxides, block polymers, carboxylated alc. or alkylphenol ethoxylates, carboxylic adds/fatty acids, cellulose derivs., ethoxylated alcs., ethoxylated alkylphenols, ethoxylated aryl phenols, ethoxylated fatty acids, ethoxylated fatty acids, ethoxylated fatty esters and oils, fatty alcs., fatty esters, glycol esters, lanolin-based derivs., lecithin and lecithin derivs., lignin and lignin derivs., Me esters, monoglycerides and derivs., phospholipids, polyacrylic acids, polyethylene glycols, polyethylene oxide-polypropylene oxide copolymers, polyethylene oxides, polymeric surfactants, polypropylene oxides, propoxylated alcs., propoxylated alkyl phenols, propoxylated fatty acids, protein-based surfactants, sarcosine derivs., silicone-based surfactants, sorbitan derivs., stearates, sucrose and glucose esters and derivs., and combinations thereof. For example, emulsion was prepared containing cyclosporin A 0.1%, castor oil 1%, clove oil 0.7%, Polysorbate-80 1%, diglycerol 0.7%, glycerin 2%, CM-cellulose 0.5%, sodium hydroxide to adjust pH (7.2) and water as needed.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 2007:58577 CAPLUS
DOCUMENT NUMBER: 146:149007
TITLE: Composition comprising cyclosporin A
INVENTOR(S): Chang, James N.; Olejnik, Orest; Firestone, Bruce A.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007008894	A2	20070118	WO 2006-US26881	20060712
WO 2007008894	A3	20070628		

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

US 20070015690	A1	20070118	US 2005-181178	20050713
US 7297679	B2	20071120		
US 20070015710	A1	20070118	US 2005-181187	20050713
US 7276476	B2	20071002		
US 20070015691	A1	20070118	US 2005-181409	20050713
US 20070015692	A1	20070118	US 2005-181428	20050713
US 7202209	B2	20070410		
US 20070015693	A1	20070118	US 2005-181509	20050713
AU 2006268264	A1	20070118	AU 2006-268264	20060712
CA 2602452	A1	20070118	CA 2006-2602452	20060712
EP 1901711	A2	20080326	EP 2006-786892	20060712
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2009501228	T	20090115	JP 2008-521528	20060712
BR 2006013533	A2	20110118	BR 2006-13533	20060712
US 20070149447	A1	20070628	US 2007-679934	20070228
US 8536134	B2	20130917		
US 20080070834	A1	20080320	US 2007-940652	20071115
US 20080207494	A1	20080828	US 2007-917448	20071213
US 8288348	B2	20121016		

PRIORITY APPLN. INFO.:	US 2005-181178	A	20050713
	US 2005-181187	A	20050713
	US 2005-181409	A	20050713
	US 2005-181428	A	20050713
	US 2005-181509	A	20050713
	WO 2006-US26881	W	20060712

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Cyclosporin A compns. are disclosed herein comprising an oil and a surfactant. These are useful in the treatment of dry eye disease. Thus, composition was prepared containing cyclosporin A 0.1, castor oil 1, clove oil 0.7, polysorbate-80 1, diglycerol 0.7, glycerin 2, CM-cellulose 0.5 and water as needed.

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

L1 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN

ACCESSION NUMBER: 2006:590857 CAPLUS

DOCUMENT NUMBER: 145:443655

TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation

AUTHOR(S): Yang, S. G.; Kim, D. D.; Chung, S. J.; Shim, C. K.

CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul, S. Korea

SOURCE: International Journal of Clinical Pharmacology and Therapeutics (2006), 44(5), 233-239
CODEN: ICTHEK; ISSN: 0946-1965

PUBLISHER: Dustri-Verlag Dr. Karl Feistle

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved phys. stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to com. available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those

obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 Healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 mL of water with a 1-wk washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment C). Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concns. using a specific monoclonal RIA. Results: The differences in bioavailability parameters (i.e., AUC0-24h, AUC0-∞ and Cmax) between the treatments were within the range of 80 - 125% of the reference treatment. An anal. of variance (ANOVA) revealed no significant differences ($p > 0.05$) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and C) were also within the criteria. Conclusion: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the com. soft capsules of CsA using a volatile cosolvent such as ethanol.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN

ACCESSION NUMBER: 2000:494420 CAPLUS

DOCUMENT NUMBER: 133:198474

TITLE: Effect of Polyoxyl 35 castor oil and Polysorbate 80 on the intestinal absorption of digoxin in vitro

AUTHOR(S): Cornaire, Gilles; Woodley, John F.; Saivin, Sylvie; Legendre, Jean-Yves; Decourt, Sylvie; Cloarec, Alix; Houin, Georges

CORPORATE SOURCE: Laboratoire de Cinetique des Xenobiotiques, Faculte des Sciences Pharmaceutiques, Toulouse, Fr.

SOURCE: Arzneimittel-Forschung (2000), 50(6), 576-579
CODEN: ARZNAD; ISSN: 0004-4172

PUBLISHER: Editio Cantor Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Surfactants are classically used to improve the solubilization of lipophilic drugs such as digoxin. Polysorbate 80 and Cremophor EL (Polyoxyl 35 castor oil) are such surfactants but they may also modulate the action of P-glycoprotein, an energy-dependent "counter-transport" system implicated in the phenomenon of multidrug resistance in cancer cells. P-glycoprotein is also present in the intestine on the apical membrane of mature enterocytes and can potentially reduce the absorption of a wide range of drugs. In this study, using the improved everted gut sac method, the effects of Polysorbate 80, Cremophor EL and cyclosporin on the absorption of digoxin were studied. An increase in the uptake of digoxin in the presence of these 3 products was shown. Cremophor EL and Polysorbate 80 had no toxic effects at the concns. used. Surfactants such as Cremophor EL and Polysorbate 80 should not only support solubilization but can also modulate the P-glycoprotein system to improve the bioavailability of poorly absorbed drugs.

OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 1996:38846 CAPLUS
DOCUMENT NUMBER: 124:66660
ORIGINAL REFERENCE NO.: 124:12317a,12320a
TITLE: Lacrimal gland-specific emulsions for topical application to ocular tissue
INVENTOR(S): Ding, Shulin; Tien, Walter L.; Olejnik, Orest
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531211	A1	19951123	WO 1995-US6302	19950517
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5474979	A	19951212	US 1994-243279	19940517
CA 2190485	A1	19951123	CA 1995-2190485	19950517
CA 2190485	C	20030415		
CA 2309033	A1	19951123	CA 1995-2309033	19950517
CA 2309033	C	20030826		
AU 9526409	A	19951205	AU 1995-26409	19950517
AU 693213	B2	19980625		
EP 759773	A1	19970305	EP 1995-921294	19950517
EP 759773	B1	20010808		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1152876	A	19970625	CN 1995-194078	19950517
CN 1229136	C	20051130		
BR 9507664	A	19971007	BR 1995-7664	19950517
JP 10500414	T	19980113	JP 1995-529895	19950517
JP 3441462	B2	20030902		
EP 1044678	A1	20001018	EP 2000-202069	19950517
EP 1044678	B1	20030312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 203911	T	20010815	AT 1995-921294	19950517
ES 2161895	T3	20011216	ES 1995-921294	19950517
PT 759773	E	20020228	PT 1995-921294	19950517
AT 234076	T	20030315	AT 2000-202069	19950517
PT 1044678	E	20030829	PT 2000-202069	19950517
ES 2194670	T3	20031201	ES 2000-202069	19950517
MX 2002000724	A	20030425	MX 2002-724	19961115
CN 1288722	A	20010328	CN 2000-120126	20000714
CN 1198587	C	20050427		
HK 1034190	A1	20051209	HK 2001-104710	20010709
GR 3036945	T3	20020131	GR 2001-401814	20011018
KR 450703	B1	20041001	KR 2001-88637	20011229
JP 2003231646	A	20030819	JP 2003-63234	20030310
JP 4119284	B2	20080716		

PRIORITY APPLN. INFO.:		
US 1994-243279	A	19940517
CA 1995-2190485	A3	19950517
EP 1995-921294	A3	19950517
JP 1995-529895	A3	19950517

WO 1995-US6302 W 19950517
KR 1996-706523 A3 19961118
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixt. with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporine A and the higher fatty acid glyceride may be castor oil. The composition allows a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues with enhanced absorption in the lacrimal gland. In addition, the composition has stability for up to 9 mo without crystallization of cyclosporin.
For example, an ophthalmic emulsion containing cyclosporin A 0.2, castor oil 2.5, Polysorbate-80 1.0, Pemulen 0.05, glycerol 2.2, NaOH q.s., and purified water to 100% was formulated to treat keratoconjunctivitis sicca.
OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 1993:588539 CAPLUS
DOCUMENT NUMBER: 119:188539
ORIGINAL REFERENCE NO.: 119:33511a,33514a
TITLE: Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components
AUTHOR(S): Pearson, Stephen D.; Trissel, Lawrence A.
CORPORATE SOURCE: Houston Biotechnol., Inc., Woodlands, TX, USA
SOURCE: American Journal of Hospital Pharmacy (1993), 50(7), 1405-9
CODEN: AJHPA9; ISSN: 0002-9289
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Diethylhexyl phthalate (DEHP) was leached from polyvinyl chloride containers by polysorbate 80, poloxyethylated castor oil, cyclosporine, miconazole, teniposide, chlordiazepoxide HCl, etoposide, and the vehicles used in the formulation of taxol and taxotere. DEHP was detectable immediately in some cases and increased in concentration over the 24-h
study period. Drugs that leach DEHP should be prepared in non-PVC containers and administered through non-PVC tubing.
OS.CITING REF COUNT: 47 THERE ARE 47 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)

L1 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2013 ACS on STN
ACCESSION NUMBER: 1993:261059 CAPLUS
DOCUMENT NUMBER: 118:261059
ORIGINAL REFERENCE NO.: 118:45259a,45262a
TITLE: Ophthalmic solutions containing cyclosporin and surfactants
INVENTOR(S): Hata, Kunio; Murano, Masaru; Ueda, Shogo
PATENT ASSIGNEE(S): Sankyo Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

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     JP 05058906          A    19930309    JP 1991-226990          19910906
PRIORITY APPLN. INFO.:                     JP 1991-226990          19910906
AB   Aqueous ophthalmic solns. contain cyclosporin (I) and surfactants chosen
     from polysorbate, polyoxyethylene hydrogenated castor oil, and
     polyoxyethylene fatty acid esters.  The solns. show good stability and do
     not irritate the eyes.  I 0.5, polyoxyethylene hydrogenated castor oil 20,
     NaCl 8 g, antiseptic, and H2O to 1000 mL were mixed to give an ophthalmic
     solution
OS.CITING REF COUNT:     2     THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
                               (2 CITINGS)


=> d his

     (FILE 'HOME' ENTERED AT 14:10:54 ON 07 OCT 2013)

     FILE 'BIOSIS, EMBASE, MEDLINE' ENTERED AT 14:16:25 ON 07 OCT 2013

     FILE 'BIOSIS, EMBASE, MEDLINE, CAPLUS' ENTERED AT 14:16:34 ON 07 OCT 2013
L1           12 (CYCLOSPORIN OR CYCLOSPORINE) (10A) ("CASTOR OIL") (10A) POLYSO

=> logoff h
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      55.99      61.82

 SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:18:02 ON 07 OCT 2013
```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 13/967,168	Group Art Unit: 1658
Filed: August 14, 2013	Confirmation No. 3265
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO NON FINAL OFFICE ACTION DATED OCTOBER 11, 2013

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

Dear Sir:

These papers are filed in reply to the Office Action mailed October 11, 2013.

Amendments to the claims begin at page 2;

Summary of the Interview begins at page 7;

Remarks follow on page 8.

AMENDMENTS TO THE CLAIMS

The following claims replace all prior versions of claims submitted in this application. Only those claims being amended herein show their changes in highlighted form, where insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g. deletions or [[deletions]]).

1. – 36. (Canceled)

37. (**Currently Amended**) A method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, ~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in increasing tear production.

38. (Previously Presented) The method of Claim 37, wherein the emulsion further comprises a tonicity agent or a demulcent component.

39. (Previously Presented) The method of Claim 38, wherein the tonicity agent or the demulcent component is glycerine.

40. (Previously Presented) The method of Claim 37, wherein the emulsion further comprises a buffer.

41. (Previously Presented) The method of Claim 40, wherein the buffer is sodium hydroxide.

42. (Previously Presented) The method of Claim 37, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

43. (Previously Presented) The method of Claim 37, wherein the emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

44. (**Currently Amended**) The method of Claim 37, wherein the emulsion comprises ~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

45. (Previously Presented) The method of Claim 37, wherein the emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

46. (Previously Presented) The method of Claim 45, wherein the buffer is sodium hydroxide.

47. (**Currently Amended**) The method of Claim 37, wherein, when the emulsion is administered to an eye of a human in an effective amount in increasing tear production ~~treating KCS~~, the blood of the human has substantially no detectable concentration of cyclosporin A.

48. (Previously Presented) The method of Claim 42, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

49. (**Currently Amended**) The method of Claim 37, wherein the emulsion is as substantially therapeutically effective as a[[n]] second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

50. (**Currently Amended**) The method of Claim 37, wherein the emulsion achieves at least as much therapeutic effectiveness as a[[n]] second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

51. (**Currently Amended**) The method of Claim 37, wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to a[[n]] second emulsion that contains only 50% as much castor oil.

52. (**Currently Amended**) The method of Claim 37, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a[[n]] second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

53. (**Currently Amended**) The method of Claim 52, wherein the adverse events are ~~include~~ side effects.

54. (**Currently Amended**) A method of treating ~~KCS~~keratoconjunctivitis sicca, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the emulsion is effective in treating ~~KCS~~keratoconjunctivitis sicca and wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

55. (Previously Presented) The method of Claim 54, wherein the buffer is sodium hydroxide.

56. (Previously Presented) The method of Claim 54, wherein the tonicity component or the demulcent component is glycerine.

57. (**Currently Amended**) The method of Claim 54, wherein, when the emulsion is administered to the eye of a human in an effective amount in treating ~~KCS~~keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of the cyclosporin A.

58. (Canceled)

59. (**Currently Amended**) A method comprising:

administering an emulsion topically to the eye of a human having ~~KCS~~keratoconjunctivitis sicca at a frequency of twice a day, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

~~Pemulen~~ acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water; and

wherein the emulsion is effective in increasing tear production in the human having ~~KCS~~keratoconjunctivitis sicca.

60. (Previously Presented) The method of Claim 59, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

An in-person interview was conducted on October 3, 2013 at the USPTO and was attended by Examiner Cordero Garcia, Laura L. Wine, Dr. Rhett Schiffman, Dr. Mayssa Attar, and Debra Condino.

Exhibits and/or Demonstrations

Data demonstrating unexpected results and commercial success of the claimed method were presented. Data and information regarding the claimed method's satisfaction of a long felt need were also presented.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37 and 54.

Identification of Prior Art Discussed

The prior art of record was discussed, focusing on Ding (U.S. Patent No. 5,474,979).

Proposed Amendments

It was proposed to amend Claims 54 to recite a range of pH in the claimed method.

Principal Arguments and Other Matters

The Applicants presented data demonstrating unexpected results, commercial success, and satisfaction of a long felt need of the claimed methods. While the Applicants do not acquiesce to any *prima facie* case of obviousness, the evidence of non-obviousness presented at the interview overcomes the *prima facie* obviousness rejection.

Results of Interview

It was agreed that the evidence of non-obviousness presented rendered the claims allowable and overcame the prior art of record. It was agreed that the Applicants would file a response, presenting data and arguments discussed at the interview.

REMARKS

This Reply responds to the Office Action sent October 11, 2013, in which the Office Action rejected Claims 37-60. Claim 58 is newly cancelled. Claims 37, 44, 47, 49-54, 57, and 59 have been amended. Thus, Claims 37-57 and 59-60 are currently pending. No new matter has been added by this amendment, and all amendments to the claims are fully supported by the originally filed application. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, second paragraph

Claims 37-60 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Applicants submit that the amendments to the claims submitted herewith render the rejection under 35 U.S.C. § 112, second paragraph moot. Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. 103(a)

The Office Action rejected Claims 37-61 under 35 U.S.C. 103(a) as being unpatentable as obvious in view of U.S. Patent No. 5,474,979 to Ding et al. ("Ding").

The Applicants submit that the *prima facie* case of obviousness has not been properly established against the pending claims. However, the Applicants submit that the unexpected results, commercial success, and satisfaction of long felt need obtained with the claimed methods and failure of others overcome the *prima facie* obviousness rejection asserted in the Office Action.

The Federal Circuit has held that objective evidence of nonobviousness must always be taken into account before a conclusion on obviousness is reached. Similarly, M.P.E.P. 716.01(a) states that "[a]ffidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-left but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the

Patent Office in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103." Thus, the *Graham* factors, including the use of objective evidence of secondary considerations to rebut a *prima facie* case of obviousness, remains the framework to be followed for a determination of obviousness. The Federal Circuit has even stated that "evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *See, Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

The Claimed Methods Provide Surprising and Unexpected Results

As discussed in the interview with the Examiner, the claimed methods provide surprising and unexpected results in view of the prior art (e.g. Ding). According to MPEP § 2144.05 (III), the Applicants can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing "(1) [t]hat the prior art taught away from the claimed invention...or (2) **that there are new and unexpected results relative to the prior art**." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004).

In support of this position, the Applicants submit herewith as Exhibit 1 a Declaration of Dr. Rhett M. Schiffman under 37 C.F.R. § 1.132 (hereinafter, "Schiffman Declaration 1"), Chief Medical Officer at Neurotech, with over 12 years of experience as a clinician in the eye care field. The Applicants also submit herewith as Exhibit 2, a Declaration of Dr. Mayssa Attar under 37 C.F.R. § 1.132 (hereinafter, "Attar Declaration"), Research Investigator at Allergan, Inc., the assignee of record of the present application, with about 15 years of experience in the pharmacokinetics field.

As described by Dr. Schiffman and Dr. Attar in their respective declarations, supported by examples and experiments, the claimed methods provided unexpected results compared to the prior art, with regards to two key objective testing parameters for dry eye or keratoconjunctivis sicca: Schirmer Tear Testing and decrease in corneal staining, and with regards to reduction in blurred vision and decreased use of artificial tears. Specifically, the claimed methods provided unexpected results compared to

formulations 1E and 1D disclosed in Ding, which included 0.05% by weight cyclosporin A and 0.625% by weight castor oil and 0.10% by weight cyclosporin A and 1.25% by weight castor oil, respectively. *See* Ding, col. 4, lines 34-43.

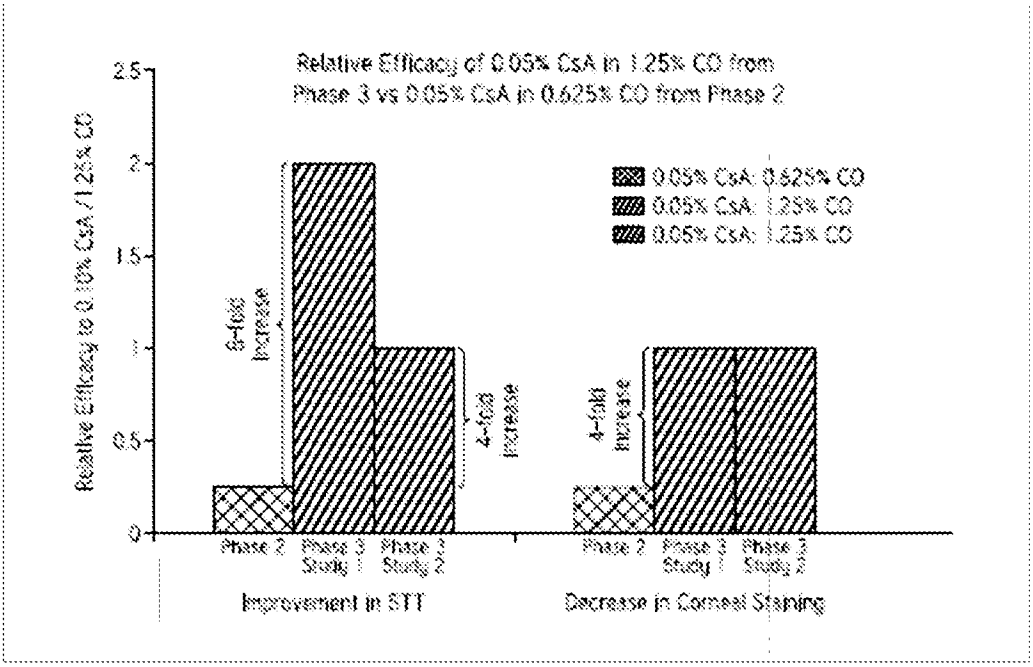
As described by Dr. Schiffman in paragraphs 17-20 of Schiffman Declaration 1 and as seen in Exhibits E and F to Schiffman Declaration 1, surprisingly, the claimed methods demonstrated an *8-fold* increase in relative efficacy for the Schirmer Tear Test ("STT") score in the first study of Allergan's Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation disclosed in Example 1E of Ding, tested in Phase 2 trials. The data presented herewith represents the subpopulation of Phase 2 patients with the same reductions in tear production (≤5 mm/5 min) as those enrolled in the Phase 3 studies. Schiffman Declaration 1 at ¶8. Exhibits E and F also illustrate that the claimed methods also demonstrated a *4-fold* improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a *4-fold* increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E). This was clearly a very surprising and unexpected result.

Exhibit E of Schiffman Declaration 1

	Phase 2 001	Phase 3 (1st study)	Phase 3 (2nd study)
	0.05% CsA in 0.625% CO	0.05% CsA in 1.25% CO	0.05% CsA in 1.25% CO
	Compared with 0.1% CsA in 1.25% CO		
Improvement in STT	0.25	2 (8-Fold Improvement*)	1 (4-Fold Improvement*)
Decrease in Corneal Staining	0.25	1 (4-Fold Improvement*)	1 (4-Fold Improvement*)

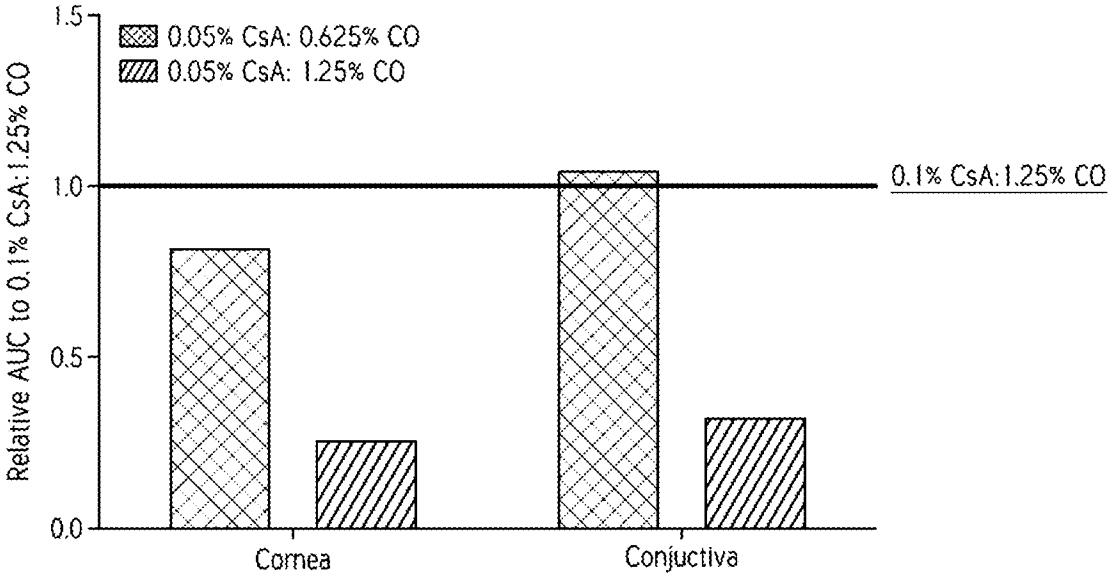
*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

Exhibit F of Schiffman Declaration 1



This dramatic increase in relative efficacy between the claimed methods and the formulation disclosed in Examples 1E and 1D of Ding was especially unexpected in view of pharmacokinetic data. As described by Dr. Attar in paragraph 7 of the Attar Declaration, pharmacokinetic studies were performed on animal eyes, which compared the pharmacokinetic properties of several cyclosporin A-containing formulations, including formulations containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil, formulations containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil, and formulations containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil. This data was compiled and organized in Exhibit B to the Attar Declaration, reproduced below:

Exhibit B to Attar Declaration



As described in paragraph 7 of the Attar Declaration, this chart shows that the amount of cyclosporin A that reaches the cornea and conjunctiva, ocular tissues that are highly relevant for the treatment of dry eye or keratoconjunctivis sicca, is higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the formulation in the claimed methods) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding 1D). According to Dr. Attar, this data teaches that the claimed methods using the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil would be less therapeutically effective than the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil or the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil. Attar Declaration at ¶ 8. Similarly, according to Dr. Schiffman, this data shows that, since lower levels of cyclosporin A were reaching the ocular tissues relevant for the treatment of dry eye, one of skill in the art would have expected patients receiving the formulation in the claimed methods to

exhibit a lesser decrease from baseline in corneal staining score and a lesser increase from baseline in Schirmer Score relative to the corneal staining scores and Schirmer Scores of the patients receiving the 0.05% by weight cyclosporin A / 0.625% by weight castor oil formulation (Ding 1E) in the Phase 2 trials, as illustrated in Schiffman Declaration 1, Exhibit B. *See* Schiffman Declaration 1 at ¶ 13.

As described by Dr. Schiffman in paragraphs 14-15 of Schiffman Declaration 1, surprisingly, the claimed method was equally or more therapeutically effective for the treatment of dry eye or keratoconjunctivitis sicca than the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding 1D) according to corneal staining score, Schirmer Score, an improvement in the common dry eye/keratoconjunctivitis sicca symptom of blurred vision and a greater decrease in the number of artificial tears used by patients.

Taking the results of the studies and data presented in the Attar and Schiffman 1 Declarations together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca.

Accordingly, the Applicants submit that the Declarations of Drs. Rhett M. Schiffman (Schiffman Declaration 1) and Attar, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed methods, including administration of a formulation with 0.05% by weight cyclosporin A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, including improved Schirmer Tear Test scores and corneal staining scores (key objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding, including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding 1D).

The Claimed Methods are Commercially Successful

As discussed during the Examiner interview, in addition to having surprising and unexpected results, the claimed methods have demonstrated commercial success. In support of this position, the Applicants submit herewith as Exhibit 3, a Declaration of Aziz Mottiwala under 37 C.F.R. § 1.132 (hereinafter, "Mottiwala Declaration"), Vice President of Marketing at Allergan for Allergan's Dry Eye Product Franchise.

As explained by Mr. Mottiwala, RESTASIS®, which is a commercial embodiment of the claimed methods, has been sold since 2003. *See* Mottiwala Declaration at ¶ 2. Since the launch of RESTASIS® in 2003, worldwide sales of the drug have increased steadily. *See* Mottiwala Declaration at ¶ 3 and Exhibit B to Mottiwala Declaration. Currently, annual world-wide net sales for RESTASIS® are over $200 million per quarter, and nearing $800 million annually. *See* Mottiwala Declaration at ¶ 4. This is strong evidence of commercial success. *See Id*. As there is no other FDA-Approved therapeutic treatment for dry eye available on the US market, RESTASIS® owns 100% of the market share. *Id*.

Accordingly, the Applicants assert that the Declaration of Aziz Mottiwala provides objective evidence that unequivocally establishes that the present invention as embodied in RESTASIS® has been met with commercial success.

The Claimed Methods Satisfied a Long-Felt Need

As discussed during the Interview, the claimed methods also resolve a long-felt need for a therapeutic treatment for dry eye or keratoconjunctivitis sicca. . In support of this position, the Applicants submit herewith as Exhibit 4, a Declaration of Dr. Rhett M. Schiffman under 37 C.F.R. § 1.132 (hereinafter, "Schiffman Declaration 2").

According to the MPEP, establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. *See* MPEP § 716.04.

First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *Id*. As explained by Dr. Schiffman, dry eye/keratoconjunctivis sicca has been a known, persistent ocular disorder for many years. Publications on dry

eye date back to at least the 1970's, and interest and publication on the subject has increased substantially since. *See* Schiffman Declaration 2 at ¶¶ 2-4.

Second, the long-felt need must not have been satisfied by another before the invention by applicant. MPEP 716.04. As explained by Dr. Schiffman, no other therapeutic dry-eye drug has been approved by the FDA before or since RESTASIS®. *See* Schiffman Declaration 2 at ¶ 8. Other treatments for dry eye, such as artificial tears, have been commercially available, but they only exhibit a palliative effect, and do not work to increase tear production or otherwise treat the disease. *See* Schiffman Declaration 2 at ¶ 4.

Third, the invention must in fact satisfy the long-felt need. MPEP 716.04. As shown by the FDA's approval of RESTASIS®, and the praise in the industry discussed by Dr. Schiffman at paragraph 8 of Schiffman Declaration 2, the claimed methods have satisfied the long felt need. As explained above, RESTASIS® has been met with great commercial success, which further shows the satisfaction of the long felt need.

Several other companies have tried to develop therapeutic drugs for FDA approval, but many have failed. *See* Schiffman Declaration 2 at ¶ 9 and Exhibit N. The Federal Circuit has implicitly accepted that failure to obtain FDA approval is relevant evidence of failure of others. *Knoll Pharm. Co. v Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

Accordingly, the Applicants assert that the second Declaration of Dr. Rhett M. Schiffman provides objective evidence that unequivocally establishes that the present invention as embodied in RESTASIS® has satisfied a long felt need and that others have failed to meet such a long felt need.

Hence, in view of the evidence presented above and presented in the attached declarations, the Applicants submit that the unexpected results, commercial success, and satisfaction of long felt need obtained from the claimed methods successfully rebut the *prima facie* case of obviousness presented in the Office Action. Thus, the Applicants respectfully request that the Examiner withdraw the outstanding rejections under 35 U.S.C. § 103.

Ding Teaches Away From the Claimed Method

The Applicants also submit that a *prima facie* case of obviousness has not been established because Ding does not disclose or suggest administering an emulsion of 0.05% cyclosporine and 1.25% castor oil at a frequency of twice a day, as required by the pending independent claims (i.e. 37, 54, and 59). Rather, Ding only discloses administration of emulsions, other than 0.05% cyclosporine and 1.25% castor oil, eight times a day for seven days. *See* Ding at col. 4, lines 31-44 and col. 5, lines 14-17.

Moreover, the Applicants also submit that one of skill in the art at the time the invention was made would not have reduced the frequency of administration of the compositions disclosed in Ding from eight times a day to twice a day because Ding teaches away from such a modification. See MPEP § 2145(X)(D).

Notably, Ding discloses that therapeutic levels of cyclosporine were reached after dosage of the Example compositions 1A-1D, which included between 0.10 – 0.40 wt% cyclosporin (higher than the currently claimed amount of cyclosporin). *See* Ding at col. 5, lines 15-23. The Applicants submit that one of skill would not be motivated to decrease both the concentration of cyclosporin and the frequency of dosage in Ding, as such a modification may not reach therapeutic levels required for successful treatment with the drug.

Thus, at least for the reasons presented above, the Applicants respectfully request that the Examiner withdraw the outstanding rejections under 35 U.S.C. § 103.

Obviousness-Type Double Patenting Rejection

Claims 37-60 were rejected for non-statutory obvious-type double patenting in view of claims 1-8 of the Ding reference.

The Applicants submit that the pending claims are patentably distinct from claims 1-8 of Ding for at least the same reasons argued above. The Applicants respectfully request, therefore, that the Office withdraw the double patenting rejection of Claims 37-60 in view of claims 1-8 of Ding.

Provisional Obviousness-Type Double Patenting Rejection

Claims 37-60 were rejected for provisional non-statutory obvious-type double patenting in view of claims 37-61 of copending U.S. Patent Application No. 13/961,818, claims 37-61 of copending U.S. Patent Application No. 13/967,179, claims 37-61 of copending U.S. Patent Application No. 13/967,163, claims 37-61 of copending U.S. Patent Application No. 13/961,828, claims 37-60 of copending U.S. Patent Application No. 13/967,189, and claims 37-60 of copending U.S. Patent Application No. 13/961,808.

While the Applicants do not necessarily agree with the provisional non-statutory obviousness-type double patenting rejections recited above, in order to expedite prosecution, terminal disclaimers in the aforementioned applications were filed on October 7, 2013. Thus, the Applicants submit that the provisional obviousness-type double patenting rejection has been rendered moot and request that this provisional obviousness-type double patenting rejection be withdrawn.

Provisional Statutory Double Patenting Rejection

Claims 37-60 were rejected for statutory double patenting in view of claims 37-60 of co-pending U.S. Patent Application No. 13/961,835. Since this is a provisional statutory double patenting rejection, the Applicants request that the Examiner allow the present case to proceed to allowance over the other aforementioned case. *See* MPEP § 804(2). The Applicants respectfully request, therefore, that the Office withdraw the provisional statutory double patenting rejection.

Conclusion

In view of the foregoing, the Applicants believe all claims now pending in the present application are in condition for allowance.

The Commissioner is hereby authorized to charge any fees required or necessary for the filing, processing or entering of this paper or any of the enclosed papers, and to refund any overpayment, to deposit account 01-0885.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (714) 246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: October 14, 2013

Laura L. Wine
Attorney of Record
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EXHIBIT 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Dr. Rhett M. Schiffman,

I, Rhett M. Schiffman, M.D., declare as follows:

1. I am currently a Vice President and Chief Medical Officer at Neurotech. I have an M.D, Masters Degrees in Clinical Research Design and Statistical Analysis and in Health Services Administration, a Bachelor's degree in Bioengineering, and over 12 years of experience in the pharmaceutical industry at Allergan, Inc. ("Allergan"). I was also a clinical investigator in the Phase 3 studies for Restasis®. I am a co-inventor on several issued patents and pending applications related to treatment methods using ophthalmic products. My *curriculum vita*, which contains a list of my publications to which I contributed, is attached to this declaration as Exhibit A.

2. I have been informed of the general nature of the rejections made by the Patent Office with respect to the previously presented claims of the above-referenced patent application and I am familiar with the references that the Patent Office has relied on in making these rejections. For example, I am aware of U.S. Patent No. 5,474,979 to Ding et al. ("Ding").

3. Restasis® is an FDA approved product that is a commercial embodiment of the invention. Specifically, Restasis® is approved as a 0.05% by weight cyclosporin ophthalmic emulsion useful for the treatment of ophthalmic conditions, such as dry eye. Specifically, Restasis® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

4. I have reviewed the pending claims in the present application, and the pending claims cover the specific formulation of Restasis® and/or the approved methods of treatment of dry eye or keratoconjunctivitis sicca for Restasis®.

5. In creating and testing the claimed methods and compositions, several unexpected benefits were discovered using the claimed compositions and/or claimed methods.

6. During development of a drug for the treatment of dry eye disease or keratoconjunctivitis sicca, Allergan performed a randomized, multicenter, double-masked, parallel-group, dose-response controlled Phase 2 trial on several cyclosporin-A and castor oil-containing formulations. In this Phase 2 study of moderate to severe KCS, the safety and efficacy of

four cyclosporin A-containing emulsion compositions were compared to one another: 0.05% by weight cyclosporin A with 0.625% by weight castor oil, 0.10% by weight cyclosporin A with 1.25% by weight castor oil, 0.20% by weight cyclosporin A with 2.5% by weight castor oil, and 0.40% by weight cyclosporin A with 5.0% by weight castor oil. A vehicle containing 2.5% by weight castor oil was also tested and compared to these formulations. In this study, patients with moderate to severe dry eye disease were treated twice daily with one of the aforementioned cyclosporin A-containing formulations or a vehicle. All of the cyclosporin A-containing formulations as well as the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate 80, 0.05% by weight Pemulen, sodium hydroxide, and water. To the best of my knowledge, the specific cyclosporin-A containing formulations tested in humans in this Phase 2 study are disclosed in the Ding reference. Results from this study illustrating the change from baseline in corneal staining and change from baseline in Schirmer Score, key objective testing measures for dry eye or KCS, are shown in Exhibit B, Figures 1 and 2, respectively.

7. As shown in Exhibit B, Figure 1, the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater decrease in corneal staining than the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation. As shown in Exhibit B, Figure 2 the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater increase in Schirmer Score (tear production) at week 12 than any other formulation tested, including the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation. Corneal staining and Schirmer score are key objective measures for determining dry eye or keratoconjunctivitis sicca disease severity.

8. After Allergan's Phase 2 study, Allergan initiated a Phase 3 study. In Allergan's multicenter, randomized, double-masked Phase 3 trials, Allergan compared the efficacy and safety of the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil to a the claimed formulation (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil), and to a vehicle containing 1.25% by weight castor oil. The data presented in Exhibit B represents the subpopulation of moderate to severe Phase 2 patients with the same reductions in tear production ($\leq$5 mm/5 min) as those enrolled in the Phase 3 studies. In this study, patients with moderate to severe dry eye disease were treated twice daily with either a formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil, a formulation containing 0.05% by weight cyclosporin and 1.25% by weight castor oil, or the vehicle. Both cyclosporin A-containing formulations and the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate 80, 0.05% by weight Pemulen, sodium hydroxide, and water.

9. I have reviewed the Declaration of Dr. Mayssa Attar ("Attar Declaration"), and I agree with her statements made in paragraphs 6-8, reproduced here. I have attached Exhibit B to the Attar Declaration to this Declaration as Exhibit C:

10. "It was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A's immunomodulatory properties to inhibit T cell activation which would lead to an increase in tear production and potentially other therapeutic effects related cyclosporine's anti-inflammatory and anti-apoptotic effects and thus limit chronic inflammation in the pathology of dry eye. To elicit it's therapeutic effect, cyclosporine must be effectively delivered to multiple target tissues of the ocular surface such as the cornea, conjunctiva, and lacrimal gland. The rate and extent at which cyclosporine is differentially delivered to the putative sites of action is critical to achieving therapeutic success in treating dry eye. Generally speaking, it was understood that pharmacokinetic/pharmacodynamic relationship would indicate that as more cyclosporin A reaches the target tissues of the ocular surface, such as the cornea and conjunctiva, the more immunomodulatory and more anti-inflammatory activity can take place and the more therapeutically effective a drug can be in treating dry eye.

11. Pharmacokinetic studies were performed on animal eyes, which compared the pharmacokinetic properties of several cyclosporin A-containing formulations. Those results are attached to this declaration in Exhibit B. As shown in Exhibit B, the relative extent at cyclosporin was absorbed increased in the relevant ocular tissues, here, the cornea and the conjunctiva, where the amount of oil present in the formulation was decreased. Specifically, the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil.

12. One of skill in the art would have understood such a result to mean that since there was more cyclosporin A present in the relevant ocular tissues in the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil and the formulation containing 0.1% by weight cyclosporine A and 1.25% by weight castor oil than the claimed formulation, that those formulations would have been more therapeutically effective than the claimed formulation. Specifically, this data suggests that the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil would have been more therapeutically effective than the claimed formulation."

13. Specifically, one of skill in the art would have expected patients receiving the claimed formulations and methods to exhibit a lesser decrease from baseline in corneal staining score and a lesser increase from baseline in Schirmer Score, relative to the patient corneal staining scores and Schirmer Scores demonstrated by the patients receiving the 0.05% by weight cyclosporin A / 0.625% by weight castor oil formulation (Ding 1E) in the Phase 2 trials illustrated in Exhibit B.

14. Surprisingly, the claimed formulation and method was equally or more therapeutically effective for the treatment of dry eye/keratoconjunctivitis sicca than the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil according to at least four testing parameters. This result was surprising and completely unexpected. These results are attached to this declaration in Exhibit D.

15. As shown in the results in Exhibit D, the claimed formulation and method was unexpectedly superior to the 0.10% by weight cyclosporin A / 1.25% by weight castor oil formulation with respect to several properties. For example, the claimed formulations and methods surprisingly exhibited a comparable or greater decrease in corneal staining score (see Exhibit D, Figure 1), a greater increase in Schirmer Score (see Exhibit D, Figure 2), an improvement in the common dry eye/keratoconjunctivitis sicca symptom of blurred vision (see Exhibit D, Figure 3) and a greater decrease in the number of artificial tears used by patients (see Exhibit D, Figure 4) compared to the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil.

16. This result was even more surprising, given earlier testing from the Phase 2 study that illustrated that compositions containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil provided more improvement in objective measures (such as corneal staining and increase in Schirmer Score – as illustrated in Exhibit B) in dry eye patients than compositions containing 0.05% by weight cyclosporin A and 0.625% castor oil.

17. I have compared the objective results showing the surprising therapeutic efficacy of the claimed formulation and method relative to the 0.10% by weight cyclosporin A and 1.25% by weight castor oil formulation tested in Phase 3 to the 0.05% by weight cyclosporin A and 0.625% by weight castor oil formulation relative to the 0.10% by weight cyclosporin A and 1.25% by weight castor oil formulation tested in Phase 2. This comparison is attached to this declaration as Exhibit E.

18. As seen in Exhibit E, in the Phase 2 study, the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding 1E) only achieved 0.25 times the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor

oil formulation and only achieved 0.25 times the decrease in corneal staining as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation. However, in the Phase 3 studies, the claimed formulation and method achieved twice the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the first study and substantially the same improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the second Phase 3 study. Also, the claimed formulation achieved substantially the same decrease in corneal staining score compared to the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation.

19. As seen in Exhibit E, and further illustrated in Exhibit F, surprisingly, the claimed formulation and method demonstrated an *8-fold* increase in relative efficacy for the Schirmer Tear Test Score in the first study of phase 3 compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding Example 1E) in the Phase 2 study. Exhibits E and F also illustrate that the claimed formulations demonstrated a *4-fold* improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a *4-fold* increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation in the Phase 2 study, the formulation disclosed in the Ding reference (Ding 1E). This was clearly a very surprising result.

20. Taking the results of these studies together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly and unexpectedly critical for therapeutic effectiveness in the treatment of dry eye/keratoconjunctivitis sicca.

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dr. Rhett M. Schiffman

Date: 10/11/13

EXHIBIT A

CURRICULUM VITAE FOR RHETT M. SCHIFFMAN, M.D., M.S., M.H.S.A.

Current Title:	Vice President and Chief Medical Officer Neurotech
Work Address:	900 Highland Corporate Drive Building #1, Suite #101 Cumberland, RI 02864
Home Address:	1843 Temple Hills Laguna Beach, CA 92651
Office Telephone:	(401) 495-2395
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Email:	r.schiffman@neurotechusa.com

EDUCATION:

Professional:	University of Michigan, School of Public Health, Ann Arbor, Michigan 2000 M.H.S.A. Health Services Administration
	University of Michigan, Rackham Graduate School, Ann Arbor, Michigan 1989 M.S. Clinical Research Design & Statistical Analysis
	Universidad Autonoma de Ciudad Juarez Instituto de Ciencias Biomedicas Juarez, Mexico 1983 M.D. Medicine
Undergraduate:	Columbia University School of Engineering and Applied Science New York, NY 1978 B.S. Bioengineering

POSTDOCTORAL TRAINING:

Fellow:	Uveitis and Ocular Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD 1996-1997
Resident:	Ophthalmology, Henry Ford Hospital, Detroit, Michigan 1993 - 1996
Resident:	Internal Medicine, Henry Ford Hospital, Detroit, Michigan 1984 - 1986
Intern:	Internal Medicine, Henry Ford Hospital, Detroit, Michigan 1983 - 1984

CERTIFICATION AND LICENSURE

Medical Licensure: California, 2002 – C50825
Michigan, 1983 - 4301046984
Board Certification: American Board of Ophthalmology, 1999; 93th percentile on Board examination
American Board of Internal Medicine, 1986; 99th percentile on Board examination

PROFESSIONAL SOCIETIES:

Member, Association for Research in Vision and Ophthalmology
American Academy of Ophthalmology
American Medical Association

PROFESSIONAL EXPERIENCE:

2013-Present	Vice President and Chief Medical Officer, Neurotech
2010-2013	Board Member, Glaucoma Research Foundation
2009-2013	Ophthalmology Therapeutic Area Head
2008-2013	Head of Development for Emerging Markets
2007-2013	Head, Global Product Enhancement/Life Cycle Management
2005-2013	Vice President, Development for Ophthalmology and Botox, Allergan Pharmaceuticals
2003-Present	Clinical Associate Professor and Attending Physician in Ophthalmology, University of California at Irvine.
2001-2005	Senior Director, Ophthalmology Clinical Research, Allergan Pharmaceuticals, Irvine, California
1999-2001	Member, Leadership Council, Eye Care Services, Henry Ford Health System, Detroit, MI
1999-2001	Director, Quality Improvement, Eye Care Services, Henry Ford Health System, Detroit, MI
1998-2001	Director of the African-American Initiative for Male Health Improvement (AIMHI). Eye Disease Screening Program in Southeast Michigan. Funded by the Michigan Department of Community Health.
1997-2001	Director of Uveitis Services, Eye Care Services, Henry Ford Health System, Detroit, MI Director of Clinical Research, Eye Care Services, Henry Ford Health System, Detroit, MI Staff Investigator, Center for Health Services Research, Henry Ford Health System, Detroit, MI
1996-2001	Reviewer to Special Study Section, National Eye Institute, National Institutes of Health, Bethesda, Maryland.
1999-2001	Director, Clinical Research, Eye Care Services, Henry Ford Hospital, Detroit, Michigan

1996-1997	Senior Staff Physician, Eye Care Services, Ophthalmology, Henry Ford Health System, Detroit, Michigan (on intergovernmental personnel act to National Eye Institute, National Institutes of Health, Bethesda, Maryland)
1994-1995	Associate Medical Director, Henry Ford Hospital Pharmacology Research Unit, Detroit, Michigan
1993-2001	Associate Research Director, Eye Care Services, Henry Ford Hospital, Detroit, Michigan
1989-2001	Staff, Center for Clinical Effectiveness, Henry Ford Hospital, Detroit, Michigan
1988-1994	Requirements Advisory Committee to the Medical Information Management System, Henry Ford Hospital, Detroit, Michigan
1989-1993	Coordinator, General Internal Medicine Research, Henry Ford Hospital, Detroit, Michigan
1990-1993	Chairman, General Internal Medicine Research Committee, Henry Ford Hospital, Detroit, Michigan
	Member, Research and Academic Affairs Committee, Department of Medicine, Henry Ford Hospital, Detroit, Michigan
1986-1993	Senior Staff Physician, General Internal Medicine, Henry Ford Hospital, Detroit, Michigan

TEACHING EXPERIENCE:

2003-Present	Ophthalmology Residency Training Program, University of California at Irvine
1997–2001	Ophthalmology Residency Training Program, Henry Ford Hospital, Detroit, Michigan
1986-1993	Internal Medicine Residency Training Program, Henry Ford Hospital, Detroit, Michigan
1988-1993	Preceptor, University of Michigan Medical Schools, Ann Arbor, Michigan
1991-1993	Preceptor, General Internal Medicine Fellows
	Medical Staff Seminars, General Internal Medicine, Henry Ford Hospital, Detroit, MI: Introduction to Epidemiology, Introduction to Personal Computing, Medical Decision Analysis

BOOKS & MONOGRAPHS:

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JOURNAL REVIEWER

1. British Journal of Ophthalmology
2. Current Eye Research
3. Ophthalmology
4. Optometry and Vision Science
5. The Lancet

SELECTED PAST SCIENTIFIC ACTIVITIES:

HFHS Principal Investigator

1. Schiffman RM, Chew E, Ferris F, Ellwein L, Hays R, Mangione C: A Randomized Comparison of the Cost, Quality and Acceptability of Four Modes of Administration the National Eye Institute Visual Functioning Questionnaire-25. National Eye Institute.

2. Schiffman RM: National Eye Institute Refractive Error Correction Questionnaire (NEI-RECQ) Phase II Protocol. National Eye Institute through Emmes Corporation.

3. Schiffman RM, Lesser GL, Imami N, Trick GL: A 48-Month, Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Clinical Study to Evaluate the Effectiveness and Safety of Oral Memantine in Daily Doses of 20 Mg and 10 Mg in Patients with Chronic Open-Angle Glaucoma at Risk for Glaucomatous Progression - Allergan Protocol 192944-005.

4. Schiffman RM: A Multicenter, Investigator-Masked, Randomized, Parallel-Group Study to Compare the Safety and Efficacy and Safety of Restasis™ (Cyclosporine 0.05% Ophthalmic Emulsion) vs. An Artificial Tear (Refresh®) Used Twice Daily for Three Months in Patients with Moderate to Severe Keratoconjunctivitis Sicca (Allergan Protocol 192371-008)

5. Schiffman RM, Patel S, Crosswell M and Shankle J: The Retinal Thickness Analyzer in the Management of Uveitic Cystoid Macular Edema.

6. Schiffman RM, Trick GL: Retinal Thickness Analyzer (RTA) - Clinical Validation Study. Talia Technology Ltd.

7. A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide Insert in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye. Bausch and Lomb.

SCIENTIFIC ACTIVITIES:

HFHS Collaborative Investigator:

1. Lesser B, Darnley D, Schiffman R: Ocular Hypertension Treatment Study. National Eye Institute, 1993- 1999.

2. Nussenblatt RB, Whitcup SM, Schiffman RM, et. al: The Treatment of Non-infectious Intermediate and Posterior Uveitis with Humanized Anti-Tac Monoclonal Antibody Therapy: Phase I and Phase II. National Eye Institute, National Institutes of Health.

EXHIBIT B

Phase 2 Results - Phase 3 Target Subpopulation

Change from Baseline in Corneal Staining at Week 12

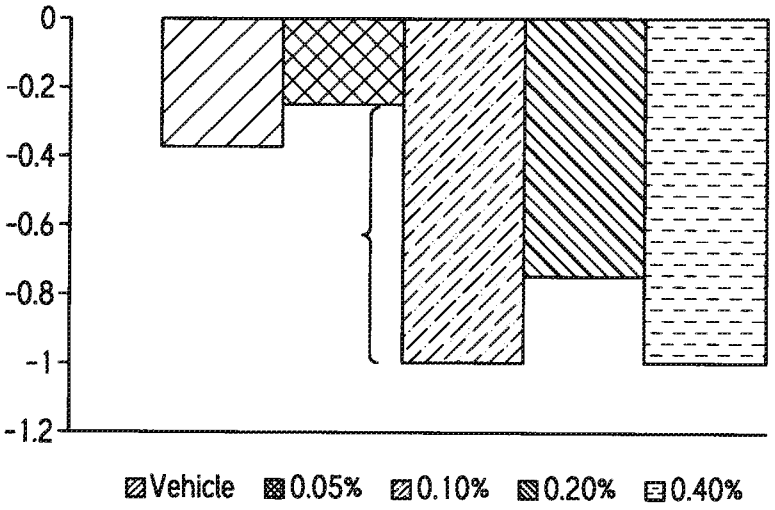


FIG. 1

Change from Baseline in Schirmer Score at Week 12

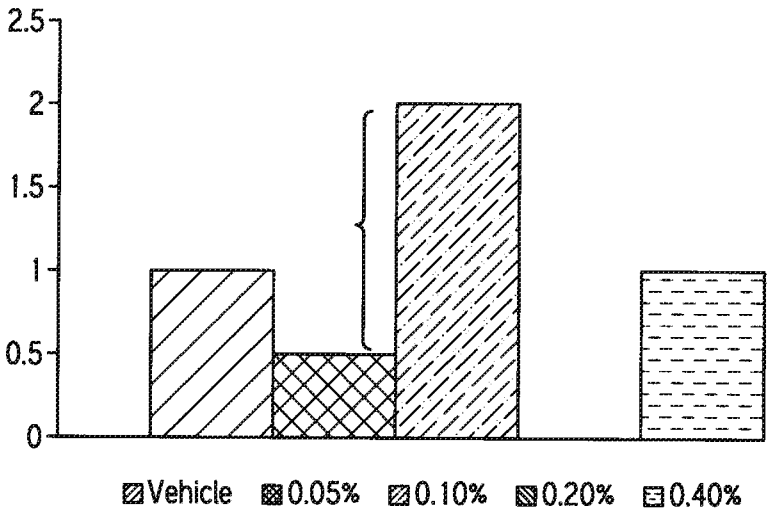


FIG. 2

EXHIBIT C

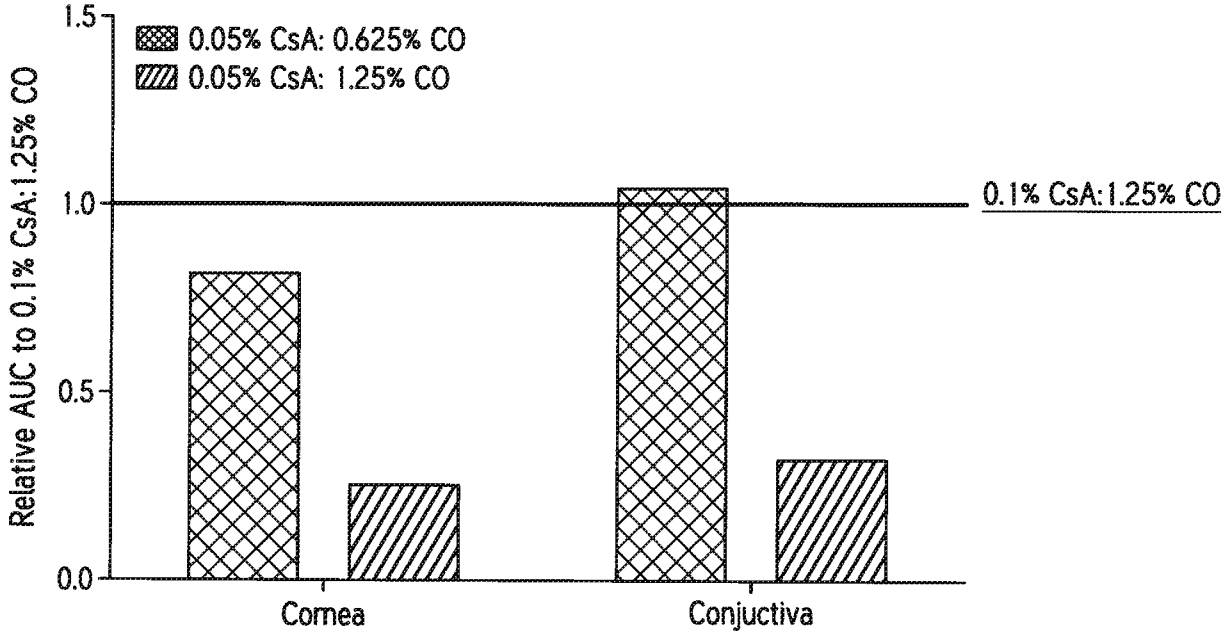

1.5
1.0
0.5
0.0
Relative AUC to 0.1% CsA:1.25% CO
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.1% CsA:1.25% CO
Cornea
Conjuctiva

EXHIBIT D

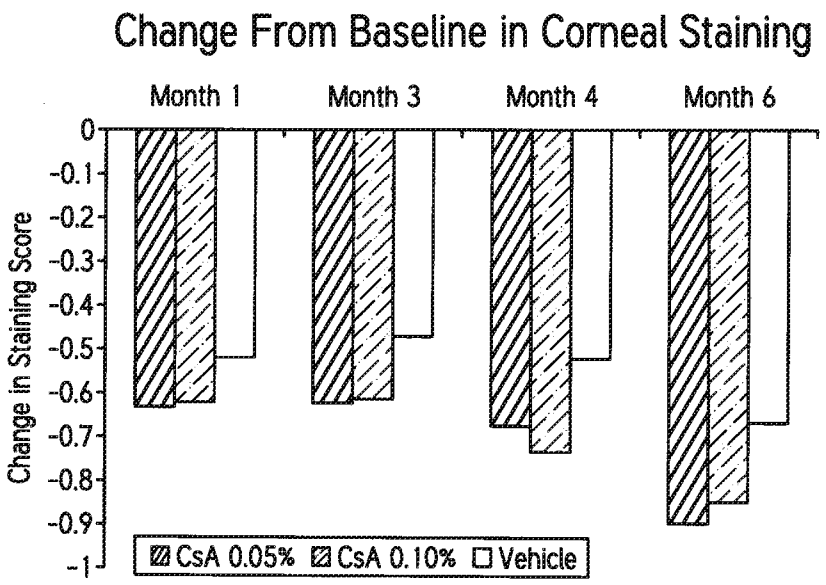

Change From Baseline in Corneal Staining
Month 1
Month 3
Month 4
Month 6
Change in Staining Score
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1
CsA 0.05%
CsA 0.10%
Vehicle

FIG. 1

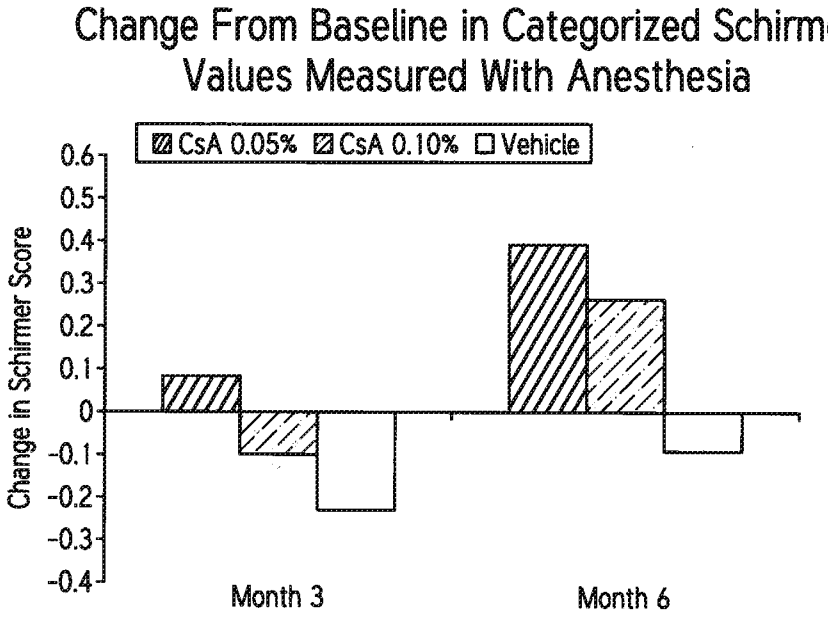

Change From Baseline in Categorized Schirmer Values Measured With Anesthesia
CsA 0.05%
CsA 0.10%
Vehicle
Change in Schirmer Score
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Month 3
Month 6

FIG. 2

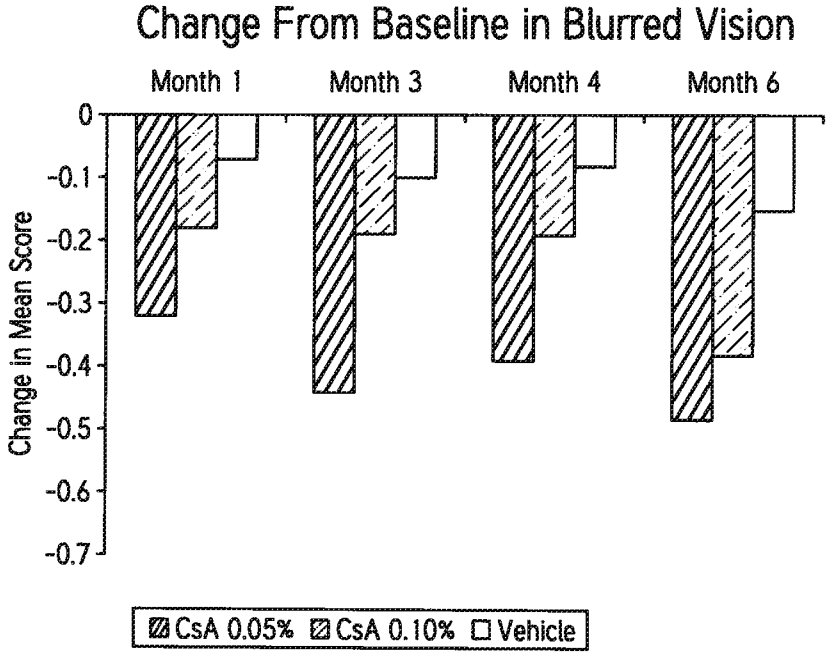

Change From Baseline in Blurred Vision
Month 1
Month 3
Month 4
Month 6
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
Change in Mean Score
CsA 0.05%
CsA 0.10%
Vehicle

FIG. 3

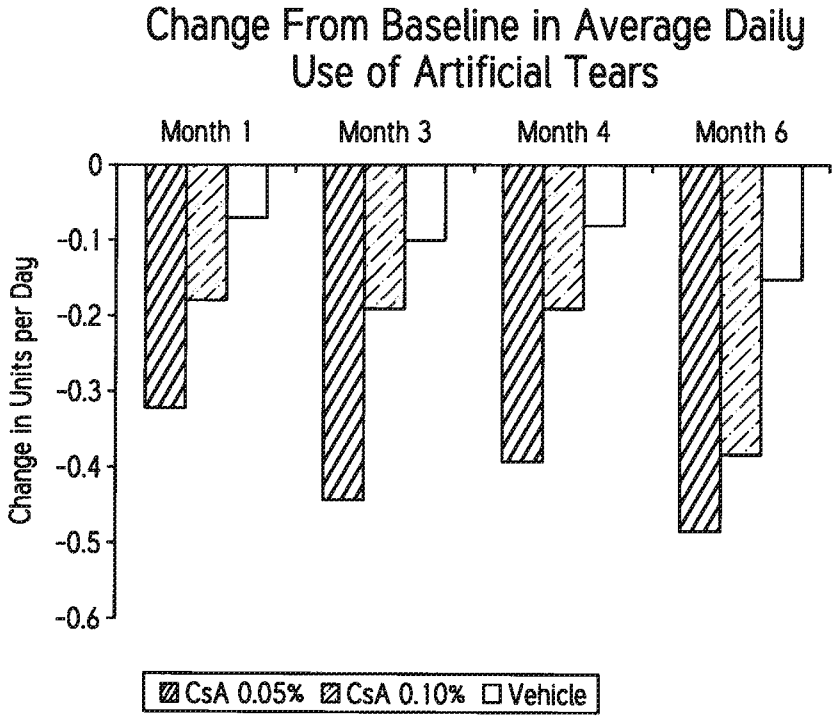

Change From Baseline in Average Daily Use of Artificial Tears
Month 1
Month 3
Month 4
Month 6
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
Change in Units per Day
CsA 0.05%
CsA 0.10%
Vehicle

FIG. 4

EXHIBIT E

	Phase 2 001	Phase 3 (1st study)	Phase 3 (2nd study)
	0.05% CsA in 0.625% CO	0.05% CsA in 1.25% CO	0.05% CsA in 1.25% CO
	Compared with 0.1% CsA in 1.25% CO		
Improvement in STT	0.25	2 (8-Fold Improvement*)	1 (4-Fold Improvement*)
Decrease in Corneal Staining	0.25	1 (4-Fold Improvement*)	1 (4-Fold Improvement*)

*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

EXHIBIT F

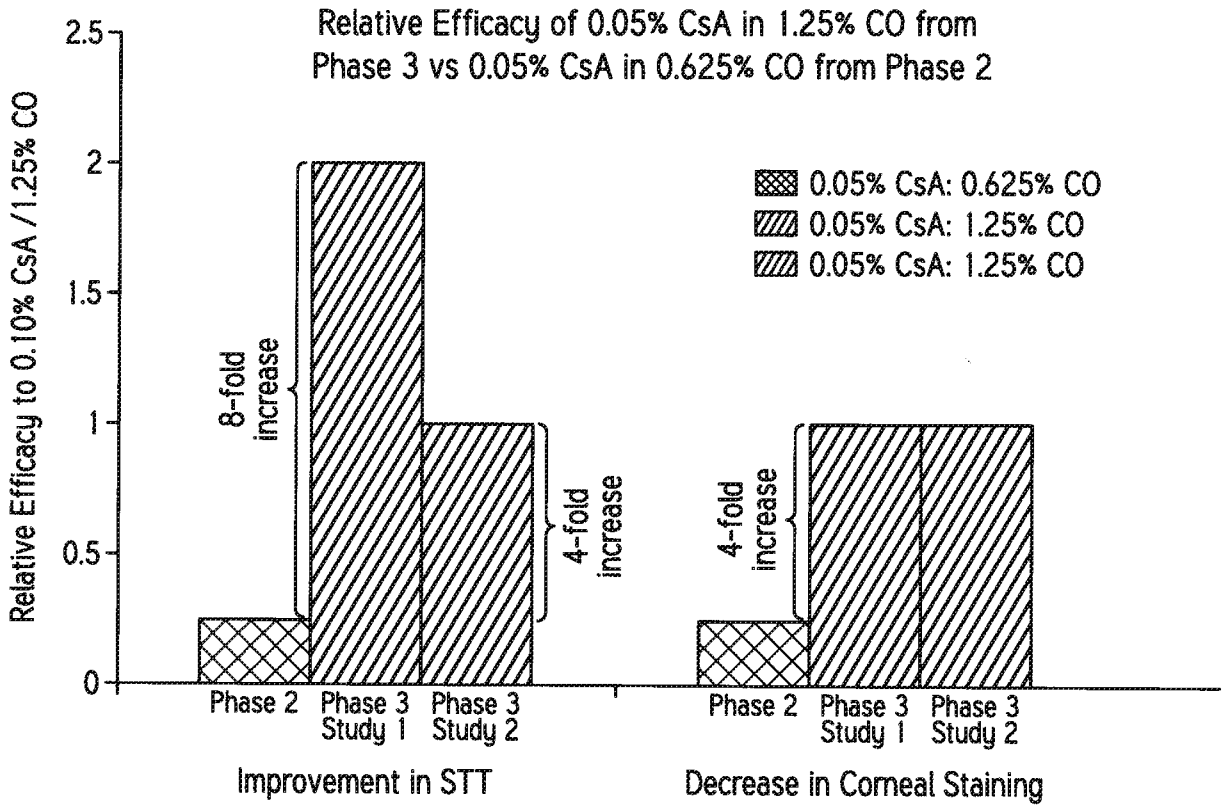

Relative Efficacy of 0.05% CsA in 1.25% CO from
Phase 3 vs 0.05% CsA in 0.625% CO from Phase 2
Relative Efficacy to 0.10% CsA /1.25% CO
2.5
2
1.5
1
0.5
0
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.05% CsA: 1.25% CO
8-fold increase
4-fold increase
4-fold increase
Phase 2
Phase 3 Study 1
Phase 3 Study 2
Phase 2
Phase 3 Study 1
Phase 3 Study 2
Improvement in STT
Decrease in Corneal Staining

EXHIBIT 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Dr. Mayssa Attar, Ph.D.

I, Mayssa Attar, Ph.D., declare as follows:

1. I am currently a Research Investigator at Allergan, Inc. ("Allergan"), specializing in preclinical and clinical pharmacokinetics and pharmacodynamics. I have a Ph.D. in Pharmaceutical Sciences, Bachelor's and Master's degrees in Biochemistry, and almost 15 years of experience in the pharmaceutical industry. I also serve as adjunct faculty at the the University of Southern California, School of Pharmacy. My *curriculum vita*, which contains a list of my publications to which I contributed, is attached to this declaration as Exhibit A.

2. I have been informed of the general nature of the rejections made by the Patent Office with respect to the previously presented claims of the above-referenced patent application and I am familiar with the references that the Patent Office has relied on in making these rejections. For example, I am aware of the "Ding" reference (U.S. Patent No. 5,474,979 to Ding et al.).

3. Restasis® is an FDA approved product that is a commercial embodiment of the invention. Specifically, Restasis® is approved as a 0.05% by weight cyclosporine ophthalmic emulsion useful for the treatment of ophthalmic conditions, such as dry eye. Specifically, Restasis® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

4. I have reviewed the pending claims in the present application, and the pending claims cover the specific formulation of Restasis® and/or the approved methods of treatment of dry eye or keratoconjunctivitis sicca with Restasis®.

5. In creating and testing the claimed methods and compositions, several unexpected results were discovered using the claimed compositions and methods.

6. It was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A's immunomodulatory properties to inhibit T cell activation, which would lead to an increase in tear production and potentially other therapeutic effects related to

cyclosporin's anti-inflammatory and anti-apoptotic effects and thus limit chronic inflammation in the pathology of dry eye. To elicit its therapeutic effect, cyclosporin must be effectively delivered to multiple target tissues of the ocular surface such as the cornea, conjunctiva, and lacrimal gland. The rate and extent at which cyclosporin is differentially delivered to the putative sites of action is critical to achieving therapeutic success in treating dry eye. Generally speaking, it was understood that pharmacokinetic/pharmacodynamic relationship would indicate that as more cyclosporin A reaches the target tissues of the ocular surface, such as the cornea and conjunctiva, the more immunomodulatory and more anti-inflammatory activity that can take place and the more therapeutically effective a drug can be in treating dry eye.

7. Pharmacokinetic studies were performed on animal eyes, which compared the pharmacokinetic properties of several cyclosporin A-containing formulations. Those results are attached to this declaration in Exhibit B. As shown in Exhibit B, the relative extent that cyclosporin was absorbed increased in the relevant ocular tissues, here, the cornea and the conjunctiva, where the amount of oil present in the formulation was decreased but the weight percentage of cyclosporin stayed the same. Specifically, the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil, relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil. We also noticed that the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil than for the claimed formulation and method.

8. One of skill in the art would have understood such a result to mean that since there was more cyclosporin A present in the relevant ocular tissues with the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil and the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil than with the claimed formulation, that those formulations would have been more therapeutically effective than the claimed formulation. Specifically, this data teaches one of skill in the art that the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil would have been more therapeutically effective than the claimed formulation.

9. Surprisingly, an unexpected increase in efficacy was demonstrated relative to the 0.1% cyclosporin A and 1.25% castor oil formulation when we compared the therapeutic efficacy of the claimed formulation and method (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil) in our multicenter, randomized, double-masked Phase

3 trials to the therapeutic efficacy of a formulation containing 0.05% by weight cyclosporin A and 0.625% cyclosporin in our a randomized, multicenter, double-masked, parallel-group, dose-response controlled Phase 2 trial.

10. As shown in Exhibits C and D, which are attached to this declaration, the corneal staining score and Schirmer scores were dramatically improved for the claimed methods (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil) compared to the formulations disclosed in Example 1E in Ding (the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil).

11. I have read the Declaration of Dr. Rhett M. Schiffman, and I agree with his statements made at paragraphs 18-19. Exhibits E and F as referenced by Dr. Schiffman are attached as Exhibits C and D:

12. "As seen in Exhibit E, in the Phase 2 study, the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding 1E) only achieved 0.25 times the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation and only achieved 0.25 times the decrease in corneal staining as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation. However, in the Phase 3 studies, the claimed formulation and method achieved twice the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the first study and substantially the same improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the second Phase 3 study. Also, the claimed formulation achieved substantially the same decrease in corneal staining score compared to the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation.

13. As seen in Exhibit E, and further illustrated in Exhibit F, surprisingly, the claimed formulation and method demonstrated an *8-fold* increase in relative efficacy for the Schirmer Tear Test Score in the first study of phase 3 compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding Example 1E) in the Phase 2 study. Exhibits E and F also illustrate that the claimed formulations demonstrated a *4-fold* improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a *4-fold* increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation in the Phase 2 study, the formulation disclosed in the Ding reference (Ding 1E). This was clearly a very surprising result."

14. Taking the results of these studies together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical

for therapeutic effectiveness for the treatment of dry eye/keratoconjunctivitis sicca, even those persons of skill in the art would have expected the formulation or method with the lower concentration of drug found in the relevant ocular tissue to be less therapeutically effective than those compositions with more drug in the ocular tissue (e.g. 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation or 0.10% by weight cyclosporin A/1.25% by weight castor oil formulation disclosed in Ding).

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 10-14-2013

Mayssa Attar, Ph.D.

EXHIBIT A

M A Y S S A A T T A R , P H D

57 Shadowbrook, Irvine, CA 92604
714-381-1853 • mayssa.attar@gmail.com
Linkedin Profile: http://www.linkedin.com/pub/mayssa-attar/13/707/b90

PROFESSIONAL SUMMARY

Almost fifteen years of drug development experience; Preclinical and clinical pharmacokinetics, pharmacodynamics, drug metabolism expertise; Oral, ophthalmic, and dermal drug development experience; Pharmacokinetics and clinical pharmacology representative supporting the submission of global regulatory filings; Cross-functional global team leader, functional line manager and matrix leader; Adjunct assistant professor at the University of Southern California, School of Pharmacy.

PROFESSIONAL EXPERIENCE

ALLERGAN • Irvine, CA• 1/1999 – present

Research Investigator, Department of Pharmacokinetics and Drug Disposition

- Serve as Group Head: Translational Sciences; Member of PK Leadership Team
- Serve as a functional line manager to PhD level scientists and cross-functional team leader on early development through market launch teams with responsibility for budgets of >$15 million
- Set departmental strategy and provide oversight to the design, conduct and data interpretation of in vitro and in vivo studies to characterize drug pharmacokinetics, pharmacodynamics and metabolism from late stage discovery through clinical development; responsible for the review of regulatory submissions
- Serve as a lead representative when interacting with global regulatory agencies for both on-site compliance inspections and regulatory file review (North America, EU, Asia-Pac and other Emerging Regions), due diligence activities, legal activities and key opinion leaders
- Serve as a team member in the development and global registration of RESTASIS®, ACUVAIL®, ZYMAXID®, OZURDEX®
- Received 6 successive promotions

UNIVERSITY OF SOUTHERN CALIFORNIA • Los Angeles, CA• 10/2005 - present

Adjunct Assistant Professor, School of Pharmacy, Department of Pharmacology and Pharmaceutical Sciences

- Lecture on the subjects of "Pharmacogenomics" and "Drug Metabolism"
- Mentor students as they consider careers in industry
- Serve as an instructor for FDA/ACCP online course "Pharmacogenomics"

LOEB RESEARCH INSTITUTE • Ottawa, ON• 6/1995 – 8/1998

Research Associate, Hormones, Growth and Development Unit

- Established protocols for isolation and purification of lipids
- Formulated liposomes as model plasma membrane systems
- FTIR-Spectroscopy, NMR

EDUCATION

PhD, Pharmaceutical Sciences, University of Southern California, Los Angeles, CA
Advisor: Vincent H L Lee, PhD, DSc
Thesis: Cytochrome P450 3A metabolism in the rabbit lacrimal gland and conjunctiva

MSc, Biochemistry, University of Ottawa, Ottawa, ON
Advisor: Nongnuj Tanphaichitr, PhD and Morris Kates, PhD
Thesis: A FTIR study of the interaction between sulfoglycolipid and phosphatidylcholine

BSc, with honors, Biochemistry, University of Ottawa, ON

AWARDS AND HONORS

- Allergan Award for Excellence, in recognition of team work to develop a pediatric investigation plan to support registration of RESTASIS® in EU (2011)
- Allergan Award for Excellence, in recognition of membership in a team charged with a departmental initiative to improve efficiencies in our Scientific Writing processes (2010)
- Allergan Award for Excellence, in recognition of collaboration with Bioanalytical Sciences to develop more efficient processes and better laboratory use of LC-MS/MS equipment to support metabolite profiling efforts (2010)
- Allergan Award for Excellence, in recognition of cost savings brought about by introducing new gene expression technology to support Toxicology assessment (2009)
- Allergan Award for Excellence, in recognition of role as Nonclinical Lead and contributing to the FDA approval and subsequent market launch of ACUVAIL™ (2009)
- Allergan Award for Excellence, in recognition of contribution to the development of an enhanced RESTASIS® formulation (2006)
- Rho Chi Honor Society (2005)
- Allergan Award for Excellence, in recognition of developing a high-throughput P450 inhibition assay (2000)
- NSERC grant to support full term of graduate studies (1996-1998)
- Travel scholarship to attend the Gordon Conference (1997)
- Loeb Summer Student Scholarship (1996)
- University Scholarships of Canada (1992-1996, awarded four consecutive years)

PROFESSIONAL AFFILIATIONS

- AAPS
- ARVO
- ISSX
- Editorial Board Member, Current Molecular Pharmacology
- Ad Hoc Reviewer Investigative Ophthalmology and Vision Science
- Ad Hoc Reviewer Journal of Pharmaceutical Sciences

OTHER SKILLS

- Computer: Watson LIMS, Phoenix/WinNonLin, Galileo LIMS, SIMCYP, Spotfire
- Languages: English, French, Arabic

PUBLICATIONS

Articles and Book Chapters

Woodward, D. F., Tang, E. S.H., Attar, M., and Wang, J. W. The biodisposition and hypertrichotic effects of bimatoprost in mouse skin. Exp Dermatol. 2013; 22:145–148.

Attar, M., Brassard, J.A., Kim, A.S., Matsumoto, S., Ramos, M., and Vangyi, C. Chapter 24: Safety Evaluation of Ocular Drugs in A Comprehensive Guide to Toxicology in Preclinical Drug Development. Edited by Faqi, A.S. Elsevier Inc., 2013

Waterbury, D.L., Galindo, D., Nguyen, C., Villanueva, L., Patel, M., Borbridge, L., Attar, M., Schiffman, R.M., Hollander, D.A. Ocular Penetration and Anti-inflammatory Activity of Ketorolac 0.45% and Bromfenac 0.09% Against Lipopolysaccharide-Induced Inflammation. J. Ocul Pharmacol Ther. 2011; 27 (2):173-8.

Chang-Lin,J., Attar, M., Acheampong, A., Robinson, M.R., Whitcup, S.M., Kuppermann, B.D., Welty, D. Pharmacokinetics and pharmacodynamics of the sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci. 2011; 52:80-86.

Attar, M., Schiffman, R.M., Borbridge, L., Farnes, Q., Welty, D. Ocular Pharmacokinetics of 0.45% Ketorolac Tromethamine. Clin Ophthalmol. 2010; 4: 1403-1408.

Attar M. and Shen J. Chapter 20: The Emerging Significance of Drug Transporters and Metabolizing Enzymes to Ophthalmic Drug Design in Ocular Transporters in Ophthalmic Diseases and Drug Delivery. Edited by Tombran-Tink, J and Barnstable, CJ. Humana Press, 2008.

Attar, M., Ling, KHJ., Tang-Liu, DDS., Neamati, N., and Lee, V.H.L. Characterization of Cytochrome P450 3A in the Rabbit Lacrimal Gland: Glucocorticoid Modulation and the Impact on Androgen Metabolism. Invest Ophthalmol Vis Sci. 2005; 46(12): 4697-4706.

Attar M., Shen, J., Ling, K.H.J, and Tang-Liu, D.D.S. Ophthalmic Drug Delivery Considerations at the Cellular Level: Drug Metabolizing Enzymes and Transporters. Expert Opin Drug Deliv. 2005; 2(5): 891-908.

Attar, M., Yu, D., Ni, J., Yu, Z., Ling, K.H.J and Tang-Liu, D.D.S. Disposition and biotransformation of the acetylenic retinoid tazarotene in humans. J Pharm Sci. 2005; 94(10): 2246-2255.

Attar, M. and Lee, V.H.L. Pharmacogenomic considerations in drug delivery. Pharmacogenomics 2003; 4(4): 443-461.

Tanphaichitr, N., Bou Khalil, M., Weerachatyanukul, W., Kates, M., Xu, H., Carmona, E., Attar, M., Carrier D. Chapter 11: Physiological and biophysical properties of male germ cell sulfogalactosylglycerolipid in Lipid Metabolism and Male Fertility. Edited by De Vriese S. AOCS Press, 2003

Attar, M., Dong, D., Ling, K.H.J. and Tang-Liu, D.D.S. Cytochrome P450 2C8 and flavin-containing monooxygenases are involved in the metabolism of tazarotenic acid in humans. Drug Metab Dispos 2003; 31(4):476-481.

Attar, M., Kates, M., Khalil, M.B., Carrier, D., and Tanphaichitr, N. A Fourier-transform infrared study of the interaction between germ-cell specific sulfogalactosylglyerolipid and phosphatidylcholine. Chem Phys Lipids 2000;106(2):101-114.

Attar, M., Wong, P.T.T., Kates, M., Carrier, D., Jacklis, P., Tanphaichitr, N. Interaction between sulfogalactosylceramide and dimyristoylphosphatidylcholine increases the orientational fluctuations of the lipid hydrocarbon chains. Chem Phys Lipids 1998; 94(2):227-238.

Tanphaichitr, N., White, D., Taylor, T., Attar, M., Rattanachaiyanont, M., and Kates, M. Role of male germ-cell specific sulfogalactosylglycerolipid (SGG) and its binding protein, SLIP1, in mammalian sperm-egg interaction in The Male Gamete: From Basic Knowledge to Clinical Applications. Edited by Gagnon, C. Cache Press, 1998

White, D., Gadella, B., Kamolvarin, N., Suwajanakorn, S., Attar, M., and Tanphaichitr, N. Role of sperm sulfogalactosylglycerolipid (SGG) on sperm-zona pellucida binding. Biol Reprod. 2000; 63(1):147-55.

Abstracts and Posters

Attar, M., Shen, J., Kim, M., Radojicic, Q.C. Cross-Species and Cross-Age Comparison of Esterase Mediated Metabolism in Vitreous: Human versus Rabbit, Dog and Monkey. Presented at ARVO Annual Meeting 2013.

Attar, M., Kim, M., Sachs, G., Scott, D., Struble, C.B., Welty, D. Modulation of Glucocorticoid Receptor Gene Expression: Potential Role in the Pharmacokinetic/ Pharmacodynamic Relationship of OZURDEX®. Presented at ARVO Annual Meeting 2011.

Attar, M., Schiffman, R.M., Borbridge, L., Farnes, Q., Welty, D. Evaluation of the Pharmacokinetics of Ketorolac Ophthalmic Solutions in Rabbit. Presented at ARVO Annual Meeting 2010.

Attar, M., Schiffman, R.M., Borbridge, L., Farnes, Q., and Welty, D. 2009 Pharmacokinetics of a Carboxymethylcellulose (CMC)-Based, Preservative-Free Formulation of 0.45% Ketorolac Tromethamine. Presented at ISOPT Annual Meeting 2009.

Wheeler, L., Robinson, M.R., Attar, M., Siemasko, K., Blanda, W., Whitcup, S.M. and Stern, M.E. 2009 Bioerodible Sustained-Release Ocular Impants in Mice Deliver Efficacious Concentrations of CsA. Presented at ARVO Annual Meeting 2009.

Yu, D., Attar, M., Parizadeh, D. and Tang-Liu, D. 2004. Pharmacokinetic Profile of Oral Tazarotene. Presented at AAD Winter 2004 meeting.

Attar, M., Lee, V.H.L., Tang-Liu, D.S. and Ling K.H.J. 2003. Characterization of Cytochrome P450 1A, 2D and 3A in the Rabbit Eye. Presented at AOPT 2003, Kona, Hawaii.

White, D., Gadella, B., Suwajanakorn, S., Kamolvarin, N., Attar, M., Abi-Khaled, L., and Tanphaichitr, N. 1997. Role of sulfogalactosylglycerolipid (SGG) in sperm-egg interaction. Presented at the Gordon Conference in Plymouth, New Hampshire.

Attar, M., Wong, P.T.T., Kates, M., Carrier, D., Tanphaichitr, N. 1997. An infrared spectroscopic study of the interaction between sulfogalactosylceramide, an analog of germ-cell specific sulfoglycolipid and phospholipid. Presented at the Gordon Conference in Plymouth, New Hampshire.

Kamolvarin, N., Suwajanakorn, S., Gadella, B., Berube, B., Attar, M., Lobsinger, D., and Tanphaichitr, N. 1996. Role of sulfogalactosylglycerolipid (SGG) on sperm-egg interaction and the zona-induced acrosome reaction (AR). Presented at the Society for the Study of Reproduction meeting in London, Ontario

Patents

Farnes, E.Q., Attar, M., Schiffman, R.M., Chang, C., Graham, R.S., Welty, D.F. Ketorolac tromethamine compositions for treating or preventing ocular pain. US Patent 7,842,714 Filed Mar 3, 2009 and Issued Dec 28, 2011.

Blanda, W.M. and Attar, M. Sustained action formulation of cyclosporin form 2. US Patent Application 13/676,551 Filed Nov 14, 2012. Patent Pending.

Morgan, A., Gore, A.V., Attar, M., Pujara, C. Cyclosporin emulsions. US Patent Application EP20110726545 Filed May 25, 2011. Patent Pending.

Attar, M., Graham, R.S., Morgan, A., Schiffman, R.M., Tien, W. Cyclosporin compositions. US Patent Application PCT/US2007/074079 Filed Jul 23, 2007. Patent Pending.

Graham, R.S., Hollander, D., Villanueva, L., Farnes, E.Q., Attar, M., Schiffman, R.M., Chang, C., Welty, D.F. Ketorolac compositions for corneal wound healing. US Patent Application EP20110715353 Filed Apr 6, 2011. Patent Pending.

Graham, R.S., Tien, W.L., Attar, M., Schiffman, R.M., Stern, M.E., Sears, R., Walt, J.G., Cassaro, T. Cyclosporin compositions for ocular rosacea treatment. US Patent Application 12/035,698 Filed Feb 22, 2008. Patent Pending.

EXHIBIT B

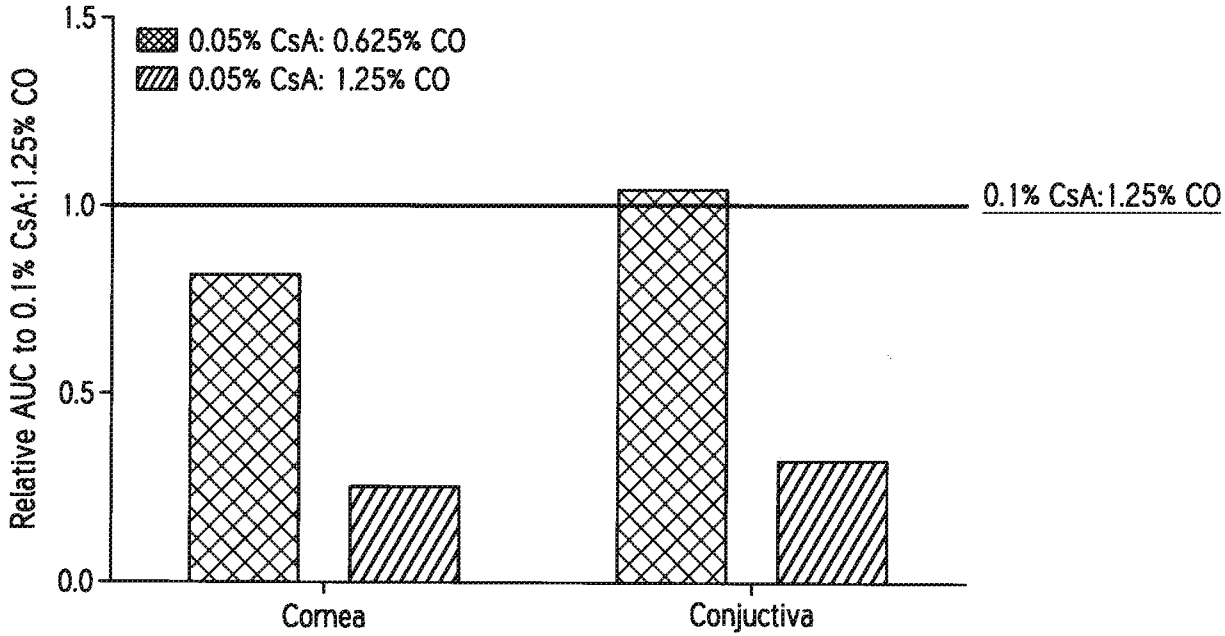

1.5
1.0
0.5
0.0
Relative AUC to 0.1% CsA:1.25% CO
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.1% CsA:1.25% CO
Cornea
Conjuctiva

EXHIBIT C

	Phase 2 001	Phase 3 (1st study)	Phase 3 (2nd study)
	0.05% CsA in 0.625% CO	0.05% CsA in 1.25% CO	0.05% CsA in 1.25% CO
	Compared with 0.1% CsA in 1.25% CO		
Improvement in STT	0.25	2 (8-Fold Improvement*)	1 (4-Fold Improvement*)
Decrease in Corneal Staining	0.25	1 (4-Fold Improvement*)	1 (4-Fold Improvement*)

*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

EXHIBIT D

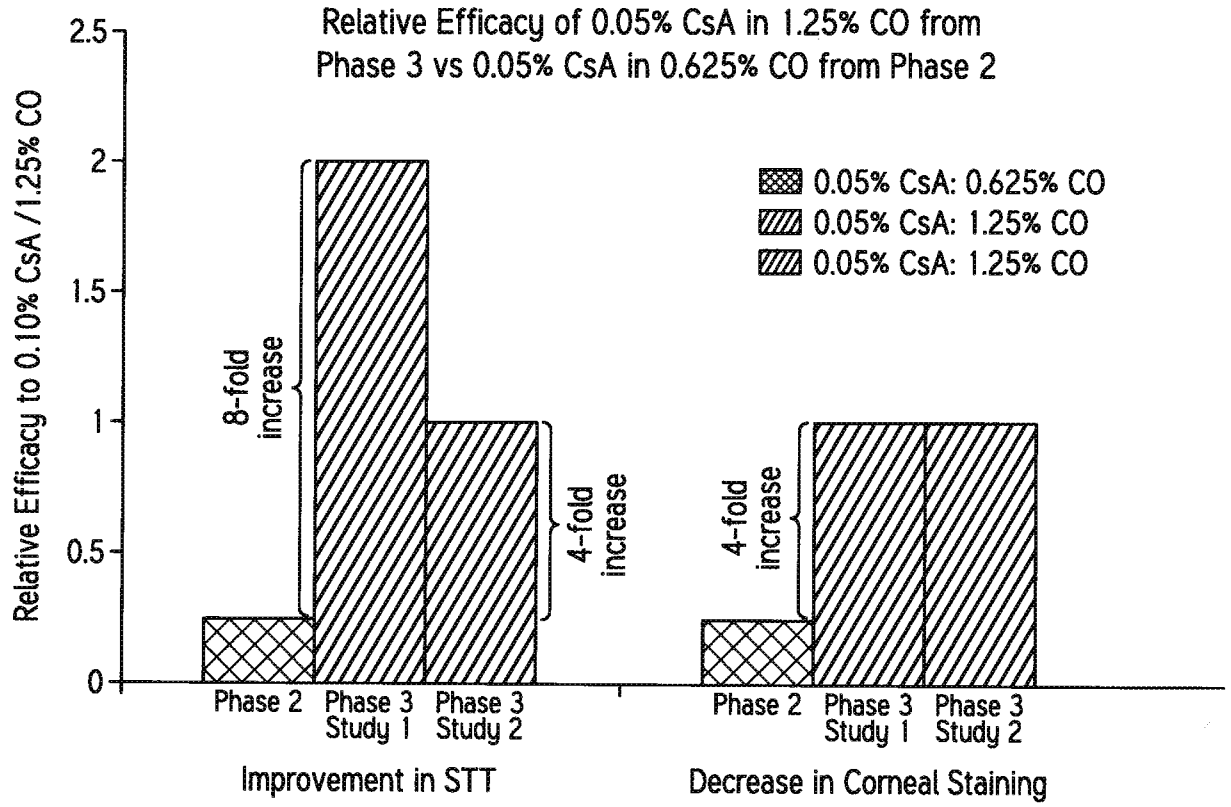

Relative Efficacy of 0.05% CsA in 1.25% CO from
Phase 3 vs 0.05% CsA in 0.625% CO from Phase 2
Relative Efficacy to 0.10% CsA /1.25% CO
2.5
2
1.5
1
0.5
0
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.05% CsA: 1.25% CO
8-fold increase
4-fold increase
4-fold increase
Phase 2
Phase 3 Study 1
Phase 3 Study 2
Phase 2
Phase 3 Study 1
Phase 3 Study 2
Improvement in STT
Decrease in Corneal Staining

EXHIBIT 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Aziz Mottiwala

I, Aziz Mottiwala, declare as follows:

1. I am currently a Vice President of Marketing at Allergan, Inc. ("Allergan") for Allergan's Dry Eye Product Franchise. I have an MBA from the University of Southern California, Marshall School of Business, a Bachelor's degree in Biochemistry, and over 15 years of experience in marketing and sales in the pharmaceutical industry. My *curriculum vita* is attached to this declaration as Exhibit A.

2. I have reviewed the pending claims in the present application, and the pending claims cover the specific formulation of Restasis® that has been sold since 2003. To the best of my knowledge, the Restasis® formulation includes 0.05% by weight cyclosporin A, 1.25% by weight castor oil, Pemulen, polysorbate 80, sodium hydroxide, and water. Restasis® was approved by the FDA on December 23, 2002.

3. Over the past ten years, Allergan has collected data on the world wide sales for Restasis® by quarter. This data is illustrated generally in Exhibit B, and broken out by country in Exhibit C, both attached to this declaration. I personally supervised the compilation of the data presented in Exhibit B and Exhibit C.

4. As illustrated in Exhibit B, the world-wide sales for Restasis® have steadily increased since the product's launch in the first quarter of 2003. Currently, annual world-wide net sales for Restasis® are over $200 million per quarter, and nearing $800 million annually. As illustrated in Exhibit C, a majority of the sales are in the US. As there is no other FDA-approved therapeutic treatment for dry eye available on the US market, Restasis® owns 100% of the market share.

5. In my expert opinion, this data is strong evidence of commercial success.

6. I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Aziz Mottiwala

Date: 10-8-13

EXHIBIT A

EDUCATION

University of Southern California, Marshall School of Business, Los Angeles, CA
Master of Business Administration (MBA), Marketing/Corporate Strategy December 2003
- Deans list: Fall 2001, Spring 2002, Fall 2002, Spring 2003, Fall 2003
- Elected to Beta Gamma Sigma National Honor Society

University of California, San Diego, Revelle College, La Jolla, CA
Bachelor of Science, Biochemistry and Cell Biology, June 1999
- Recipient, American Society of Pharmacology and Experimental Therapeutics Research Fellowship.
- Howard Hughes Research Scholar, UCSD School of Medicine, Department of Pharmacology.

EXPERIENCE.

Allergan Inc., Irvine, CA

Vice President, Dry Eye Marketing
February 2013- Current
Leading all strategic development and professional promotions across Allergan's Dry Eye product franchise. Providing strategic direction over both Dry Eye promotions and strategic communications. Also, providing leadership and direction for all key brand forecasts and budgets. Leading long term strategic planning and budgeting, as well as implementation of key marketing plans to exceed corporate financial targets.

Marketing Director, Dry Eye
August 2010- February 2013
Leading all strategic development and professional promotions across Allergan's Dry Eye product franchise. Providing strategic direction over both Dry Eye promotions and strategic communications. Also, providing leadership and direction for all key brand forecasts and budgets. Leading long term strategic planning and budgeting, as well as implementation of key marketing plans to exceed corporate financial targets.

Product Director, Restasis® *Professional Marketing*
October 2009- August 2010
Professional Promotions across Allergan's Dry Eye product franchise. Providing strategic direction over both Dry Eye promotions and strategic communications. Also, providing leadership and direction for all key brand forecasts and budgets.

Sr. Manager Restasis® *Consumer Marketing*
October 2007- October 2009
Managed Consumer Promotions across Allergan's Dry Eye product franchise. Responsible for Restasis® Direct-to-Consumer initiatives, including TV, Print and Interactive strategies and media planning. Also directing strategies and tactics for Dry Eye Franchise CRM, and Compliance/Persistency programs.

Product Manager Restasis®/Optometric Strategies
December 2006- October 2007
Developed and implemented marketing plans for Optometric strategies in Dry Eye as well as other therapeutic areas within US Eye Care. Worked with the entire marketing team to drive brand strategy and ensure proper execution of tactics. Also managed brand forecasts and budgets, to ensure proper alignment of resources across the brand team.

IMS/Cambridge Management Consulting, El Segundo, CA

Sr. Consultant, Management Consulting
July 2006- December 2006
Managed project teams including both internal and external resources in the design, development and delivery of client solutions. Provided coaching and direction to Consultants across multiple projects at any given time. Led teams to review and analyze client requirements, and developed associated proposals that ensured profitability and high client satisfaction.

- Projects across several practice areas including Pricing and Reimbursement, Portfolio Development, and Sales Force Effectiveness.
- Assisted a mid size biotech company's business development team in the assessment of several acquisition opportunities.
- Key Projects included development of a commercialization/launch playbook for a startup biotech company, as well as extensive pricing and reimbursement analysis of a Phase III product for a major biotech firm.

EXPERIENCE (continued)

Valeant Pharmaceuticals, Costa Mesa, CA

Product Manager, Neurosciences/Hepatology
September 2004-July 2006
Managing the development, market analysis and implementation of marketing plans for Tasmar®, Zelapar®, and most recently Infergen®. Driving brand strategy and ensuring proper execution of tactics. Also the primary marketing contact for field sales, providing marketing support to promote sales growth. Developing brand budgets and monitoring annual expense requirements, to ensure optimum utilization of marketing resources.

- Partnered with Business Development to acquire and transition marketing of Infergen® for Hep- C
- Produced new promotional materials and tactical programs such as sampling, and speaker programs to support strategy and drive sales.
- Developed Pre-Launch market research plan for Zelapar®. Including message testing, concept testing, and forecast development.
- Managed key medical education initiatives, including KOL Advisory boards, major conference symposia, publications and various CME programs.

Analyst, Global Marketing/Commercial Development
September 2003-September 2004
Supported Global Marketing and Development with market analysis and forecasting expertise that integrated secondary data sources and primary market research. Utilized IMS data to develop and execute integrated marketing analysis plans and product forecasts.

- Led the planning and execution of multi-attribute qualitative and quantitative market research projects for development products.
- Developed KOL targeting strategy for Viramidine, a Phase III product for Hepatitis C.
- Developed product forecasts and financial valuation models for business development during the acquisitions of Amarin Corp. and Xcel Pharmaceuticals, as well as the acquisition of Tasmar®, an in-line product for Parkinson's disease.

Aventis Pharmaceuticals, Bridgewater, NJ

Area Sales Manager (Interim)
August 2002-September 2003
Managed a team of 10 sales associates in the Southern California area. Provided guidance on selling strategies and tactics as well as communicating and implementing key marketing initiatives.

- District Ranking increased from 6 to 2 among 8 districts in a 12-month period.
- Developed nationally implemented ROI tool for sales associates to measure success of promotional programs.

Professional Sales Associate/Field Sales Trainer
September 1999- August 2002
Successfully marketing and increasing market share for therapeutic products for various disease states. Developing specialists as advocates to ensure maximum product pull through, resulting in yearly sales attainment over 100%. Trained 10 new sales associates on product knowledge and selling skills.

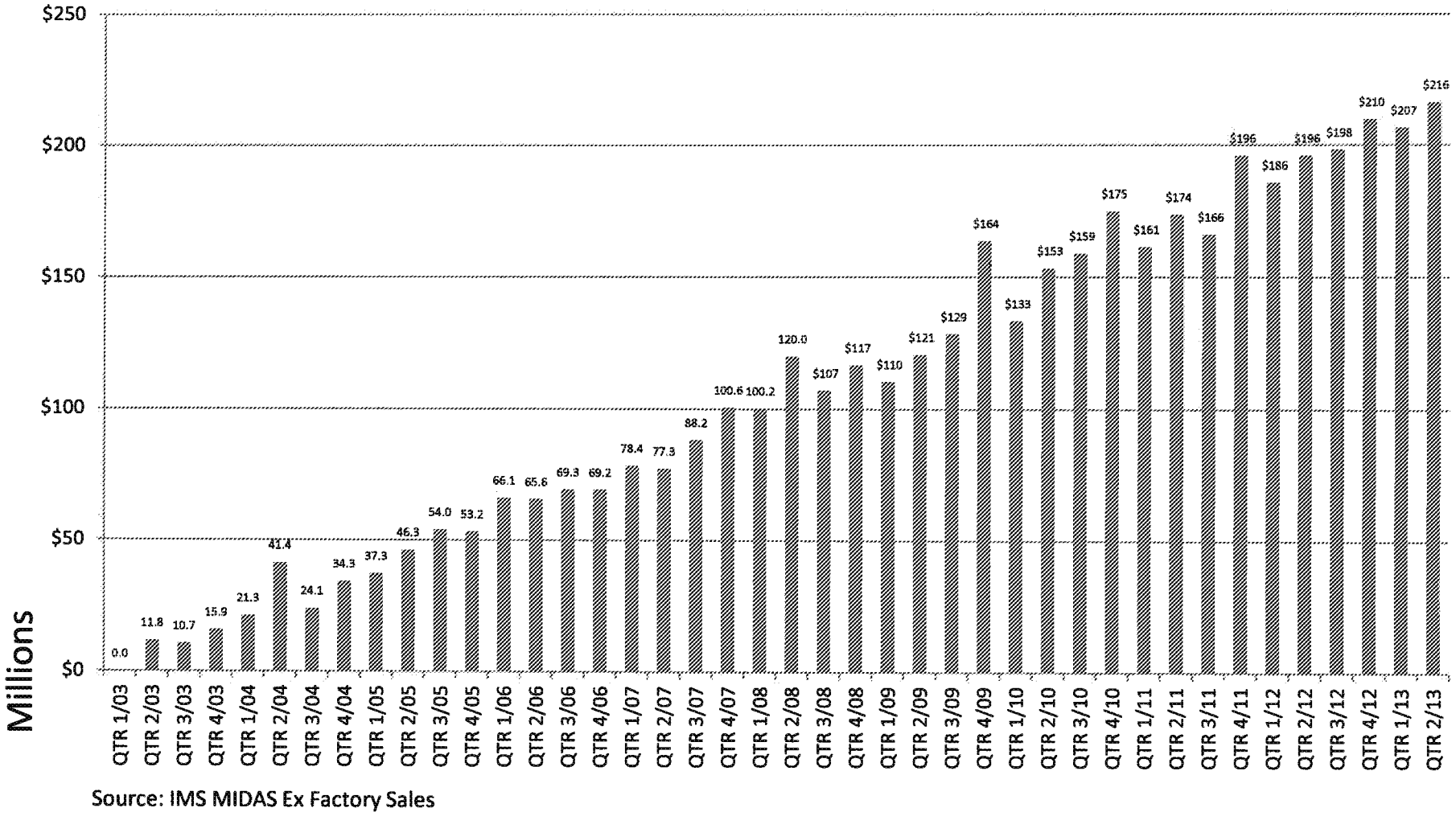
- Experience selling therapeutic products in various disease states including: Allergy, Asthma, Diabetes, Arthritis and Osteoporosis.
- Nova Award 2000: National award recognizing outstanding sales performance for a new associate.

Saier Lab, U.C. San Diego Department of Biology, La Jolla, CA
Research Associate
September 1998-June 1999

Printz Lab, U.C. San Diego School of Medicine, La Jolla, CA
Research Associate
December 1997-February 1999
Contributed to three separate research projects addressing genetics, neurology, and psychiatry. Contributed work to a major journal for publication: Palmer, A.; Dulawa, S.C.; **Mottiwala, A.A.;** Printz, M.P. "Pre-pulse Inhibition of the Air Puff Startle Response in Four Strains of Rats" *Behavioral Neuroscience* 2000 Apr;114(2):374-88

EXHIBIT B

World Wide RESTASIS Sales by QTR 2003-2013 YTD



Source: IMS MIDAS Ex Factory Sales

EXHIBIT C

EXHIBIT 4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Dr. Rhett M. Schiffman

I, Rhett M. Schiffman, M.D., declare as follows:

1. I am currently a Vice President and Chief Medical Officer at Neurotech. I have an M.D., Masters Degrees in Clinical Research Design and Statistical analysis and in Health Services Administration, a Bachelor's degree in Bioengineering, and over 12 years of experience in the pharmaceutical industry at Allergan, Inc. ("Allergan"). I am a co-inventor on several issued patents and pending applications related to treatment methods using ophthalmic products. My *curriculum vita*, which contains a list of my publications to which I contributed, is attached to this declaration as Exhibit A.

2. Dry eye disease, also named keratoconjunctivitis sicca, is among the leading causes of patient visits to ophthalmologists in the United States. This condition has been recognized by the medical community and studied for decades. In the 1970s, over 600 articles were published on dry eye syndrome. The number of articles increased to over 1400 in the 1980s, over 2500 in the 1990s, and over 4800 in the last decade and counting.[1] It is estimated that at least twenty-three million Americans suffer from dry eye disease, which has two main causes: decreased secretion of tears by the lacrimal (tear-producing) glands, and loss of tears due to excess evaporation. Both causes lead to ocular discomfort, often described as feelings of dryness, burning, a sandy/gritty sensation, or itchiness. Symptoms, such as visual fatigue, sensitivity to light, and blurred vision also are characteristics of the disease. This is a serious disorder that, if left untreated or undertreated, progressively damages the ocular surface, and may lead to vision loss.

3. Dry eye disease is a disorder of the "tear film,"[2] and ocular inflammation is known to play a major role in the symptoms and progression of the disease. Dry eye disease patients can suffer mild irritation (Level 1 severity). In patients with Level 2 to Level 4

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[1] Galor et al. (2012), attached as Exhibit B.

[2] The eye surface is supported and maintained by the tear film, which is composed of three components (lipid, aqueous, and mucin) that make up two fluid layers . Normal healthy tears contain a complex mixture of proteins and other components that are essential for ocular health and comfort. Tears provide nutrients and support the health of cells in the cornea, lubricate the ocular surface, and protect the exposed surface of the eye from infections. Clear vision depends on an even distribution of tears over the ocular surface. Dry eye disease affects the eye surface and changes the tear film composition dramatically. Typical changes include an elevated tear osmolarity, aqueous deficiency, altered mucins and lipid layer, and an altered proteomic profile.

severity scores, the symptoms are quite debilitating.[3] If the condition in these cases is untreated or treated inadequately (e.g., only with an agent such as artificial tears), the disease will continue to progress, and will lead to severe eye damage and vision loss.[4] Severe problems with untreated dry eye can also lead to corneal infection and scarring. Compared across different diseases, dry eye was found to cause degradation in quality of life that is on par with other severe disorders, such as class III/IV Angina.[5]

4. At the time Allergan initiated the Restasis® development program in 1992, dry eye was a well-recognized largely unmet medical condition. No therapeutic treatments were available, apart from the use of artificial tears, which had no direct pharmacology effect, and, blockage of the lacrimal drainage system with punctal plugs or cauterization for the most severe cases, which as we have since learned, made many patients worse by keeping the inflamed tears in constant contact with the ocular surface. In addition, neither artificial tears nor punctual plugs or cauterization actually worked to increase normal tear production in patients suffering from dry eye. Also, a 2002 Gallup poll data where 501 dry eye sufferers were interviewed predating the launch of Restasis®, showed that patients suffering from dry eye were looking for convenient and effective treatment for dry eye that provided long-lasting relief.[6] Almost 74% of consumers polled in 2002 wished there was a more effective treatment for dry eye.[7]

5. Allergan's investigators completed seminal work in the dry eye disease area, identifying the role of the T-cell and chronic inflammation in the pathogenesis of dry eye disease,[8] followed by application of cyclosporine (a drug previously used systemically to prevent transplant rejection) to target the disease locally. However, the lipophilic nature of cyclosporine made it extremely difficult to formulate an ocular-friendly preparation with good bioavailability. The multiple target tissues of the ocular surface (cornea, conjunctiva, lacrimal glands, etc.), the composition of the tear film (not a simple salt solution), and the short retention time on the eye contributed many complex issues in creating an efficacious formulation. Various formulations were attempted with

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[3] Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. Cornea. 2006;25:900-07, attached hereto as Exhibit C; Dry Eye Workshop. Management and therapy of dry eye disease: report of the management and therapy subcommittee of the international dry eye workshop. Ocul Surf. 2007a;5:163-78, attached hereto as Exhibit D.

[4] Rao S. Topical cyclosporine 0.05% for the prevention of dry eye disease progression. J Ocular Pharmacol Thera. 2010;26:157-163, attached hereto as Exhibit E; Deschamps N., Ricaud X., Rabut G., Labbé A., Baudouin C., Denoyer A. The impact of dry eye disease on visual performance while driving. Am J Ophthalmol. 2013; 125:184-189, attached hereto as Exhibit F.

[5] Schiffman R.M., Walt J.G., Jacobsen G., Doyle J.J., Lebovics G., Sumner W. Utility assessment among patients with dry eye disease. Ophthalmology. 2003;110:1412-1419, attached hereto as Exhibit G.

[6] The 2002 Gallup Study of Dry Eye Sufferers, attached hereto as Exhibit H.

[7] *Id.*

[8] Stern M.E., Beuerman R.W., Fox R.I., Gao J., Mircheff A.K., Pflugfelder, S.C. A unified theory of the role of the ocular surface in dry eye. Adv Exp Med Biol. 1998;438:643-51, attached hereto as Exhibit I.

concentrations up to 2% w/v cyclosporine and were poorly tolerated and absorbed. Ultimately, Allergan successfully formulated Restasis® in its current form, as presently claimed in the current patent application.

6. The approved Restasis® indication was based on statistically significant benefits in each of two pivotal clinical studies in which efficacy was defined as an improvement in the amount of tears produced (measured with a Schirmer score with anesthesia of $\geq$ 10 mm / 5 min, from a baseline of 0-5 mm). As a normal value for Schirmer's wetting is 10 mm / 5 min, an improvement of $\geq$ 10 mm / 5 min assured that responders achieved a total reversal of this measure of disease (i.e., a complete response) regardless of their baseline measurements. Patients in these trials suffered from moderate to very severe dry eye symptoms, with 60% of the patients scored as having the most severe Level 4 symptoms (discussed further below). Despite the severity of disease at baseline, and the very high hurdle for success, the proportion of patients experiencing complete response was three-fold higher among subjects taking Restasis® compared with those taking vehicle after 6 months of treatment. This was a highly significant result ($p<.007$).

7. The improvement in symptoms continued for 12 months and beyond in both the Restasis® group and in vehicle treated patients who were switched to Restasis® at month 6. It should be noted that these trials were begun in the late 1990s and were the first of their kind.

8. Restasis® was FDA approved on December 23, 2002. The approval of Restasis® for the treatment of dry eye represented a major paradigm shift in the treatment of dry eye.[9] Restasis® was the first FDA approved prescription medication for dry eye, and is still the only FDA approved prescription medication for dry eye. Restasis® has been well received by the medical community as a major breakthrough in dry eye treatment, and is currently the #1 selling eye drop in the world. For example, Dr. Henry Perry stated that "[i]t is important in any type of chronic ocular surface disease, especially due to aqueous deficiency, to begin topical cyclosporine."[10] Another physician, Dr. Christopher Starr stated "'I liked Restasis from the beginning and I have increased my prescribing of it over the years as I've gained more experience and witnessed its impressive results," and "[t]he most recent definition of dry eye disease from the Dry Eye WorkShop (DEWS) report notes hyperosmolarity and inflammation as key pathophysiologic factors, which a recommends the use of anti-inflammatory medication such as Restasis beginning with level 2 disease."[11]

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[9] Pflugfelder, 2006 attached as Exhibit J.

[10] Ocular Surgery, January 2013, attached as Exhibit K.

[11] Ophthamology Management, September 2013, attached as Exhibit L.

9. Other companies have tried to develop prescription treatments for dry eye, but none have been FDA approved as of this date.[12] A partial listing of companies and drugs for drug eye that have failed are attached hereto as Exhibit N. One example of such drug is Prolacria, a dry eye treatment that was developed for over a decade by Inspire Pharmaceuticals, but was cancelled in 2010 when Prolacria failed to outperform a placebo in their phase III clinical trials.[13]

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12 http://www.ophthalmologymanagement.com/articleviewer.aspx?articleid=104917 accessed 2013-09-24 and attached as Exhibit M.

13 http://www.bizjournals.com/triangle/stories/2010/08/23/daily11.html?page=all accessed 2013-09-24 and attached as Exhibit O.

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dr. Rhett M. Schiffman

Date: 10/11/13

EXHIBIT A

CURRICULUM VITAE FOR RHETT M. SCHIFFMAN, M.D., M.S., M.H.S.A.

Current Title:	Vice President and Chief Medical Officer Neurotech
Work Address:	900 Highland Corporate Drive Building #1, Suite #101 Cumberland, RI 02864
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BOOKS & MONOGRAPHS:

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JOURNAL REVIEWER

1. British Journal of Ophthalmology
2. Current Eye Research
3. Ophthalmology
4. Optometry and Vision Science
5. The Lancet

SELECTED PAST SCIENTIFIC ACTIVITIES:

HFHS Principal Investigator

1. Schiffman RM, Chew E, Ferris F, Ellwein L, Hays R, Mangione C: A Randomized Comparison of the Cost, Quality and Acceptability of Four Modes of Administration the National Eye Institute Visual Functioning Questionnaire-25. National Eye Institute.

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3. Schiffman RM, Lesser GL, Imami N, Trick GL: A 48-Month, Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Clinical Study to Evaluate the Effectiveness and Safety of Oral Memantine in Daily Doses of 20 Mg and 10 Mg in Patients with Chronic Open-Angle Glaucoma at Risk for Glaucomatous Progression - Allergan Protocol 192944-005.

4. Schiffman RM: A Multicenter, Investigator-Masked, Randomized, Parallel-Group Study to Compare the Safety and Efficacy and Safety of Restasis™ (Cyclosporine 0.05% Ophthalmic Emulsion) vs. An Artificial Tear (Refresh®) Used Twice Daily for Three Months in Patients with Moderate to Severe Keratoconjunctivitis Sicca (Allergan Protocol 192371-008)

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6. Schiffman RM, Trick GL: Retinal Thickness Analyzer (RTA) - Clinical Validation Study. Talia Technology Ltd.

7. A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide Insert in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye. Bausch and Lomb.

SCIENTIFIC ACTIVITIES:

HFHS Collaborative Investigator:

1. Lesser B, Darnley D, Schiffman R: Ocular Hypertension Treatment Study. National Eye Institute, 1993- 1999.

2. Nussenblatt RB, Whitcup SM, Schiffman RM, et. al: The Treatment of Non-infectious Intermediate and Posterior Uveitis with Humanized Anti-Tac Monoclonal Antibody Therapy: Phase I and Phase II. National Eye Institute, National Institutes of Health.

EXHIBIT B

Dry Eye Medication Use and Expenditures: Data From the Medical Expenditure Panel Survey 2001 to 2006

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Purpose: To study dry eye medication use and expenditures from 2001 to 2006 using a nationally representative sample of US adults.

Methods: This study retrospectively analyzed dry eye medication use and expenditures of participants of the 2001 to 2006 Medical Expenditure Panel Survey, a nationally representative subsample of the National Health Interview Survey. After adjusting for survey design and for inflation using the 2009 inflation index, data from 147 unique participants aged 18 years or older using the prescription medications Restasis and Blephamide were analyzed. The main outcome measures were dry eye medication use and expenditures from 2001 to 2006.

Results: Dry eye medication use and expenditures increased between the years 2001 and 2006, with the mean expenditure per patient per year being \$55 in 2001 to 2002 (n = 29), \$137 in 2003 to 2004 (n = 32), and \$299 in 2005 to 2006 (n = 86). This finding was strongly driven by the introduction of topical cyclosporine emulsion 0.05% (Restasis; Allergan, Irvine, CA). In analysis pooled over all survey years, demographic factors associated with dry eye medication expenditures included gender (female: \$244 vs. male: \$122, $P < 0.0001$), ethnicity (non-Hispanic: \$228 vs. Hispanic: \$106, $P < 0.0001$), and education (greater than high school: \$250 vs. less than high school: \$100, $P < 0.0001$).

Conclusions: We found a pattern of increasing dry eye medication use and expenditures from 2001 to 2006. Predictors of higher dry eye medication expenditures included female gender, non-Hispanic ethnicity, and greater than a high school education.

Key Words: dry eye syndrome, Medical Expenditure Panel Survey, MEPS, expenditures

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Dry eye syndrome (DES) has recently gained recognition as a public health problem.[1–3] In the decade between 1970 and 1980, 670 articles were published on DES (search terminology dry eye syndrome, limits humans, and English); this increased to 1485 articles in the 1980s, 2511 articles in the 1990s, and 4887 articles in the last decade. Part of this recognition came from several US population–based and international population–based studies demonstrating that the condition was present in between 5% and 30% of the population aged 50 years or older.[1,2,6–17] Another part of the recognition came from understanding that the symptoms of DES, which include constant irritation, foreign body sensation, and blurred vision, interfere with the ability to work and carry out daily functions.[18–20] A study using the Impact of Dry Eye Living Questionnaire found that severe dry eye symptoms were correlated with difficulties in physical, social, and mental functioning.[21] Such difficulties translate into a relatively lower health-related quality of life compared with the general population—patients with severe dry eye symptoms have health-related quality of life scores in the range of conditions like class III/IV angina.[20]

An additional event that helped push DES into the limelight was the release of the first Food and Drug Administration–approved prescription medication for DES, cyclosporine emulsion 0.05% (Restasis; Allergan, Irvine, CA). The Food and Drug Administration approved the medication in 2002, and the pharmaceutical company Allergan launched cyclosporine emulsion in the United States in late 2003. As part of its sales strategy, Allergan used direct to consumer marketing and commissioned magazine and television advertisements to reach its target audience; it also heavily promoted cyclosporine emulsion within the eye care community. These activities had the effect of increasing physician and patient awareness of the prevalence of DES, its morbidity, and its potential treatments.

Although there is a sense that the economic implications of DES are substantial, few articles have studied the direct costs associated with DES and other ocular surface disorders. These include costs associated with office visits, prescription medication, over-the-counter medication, alternative or complementary medication, and nonpharmacologic purchases (eg, humidifiers). A retrospective claims analysis evaluating costs in 9065 patients who received topical cyclosporine for DES found a mean health care cost of \$336 per patient with a total cost of \$3.05 million.[22] A retrospective analysis of the annual cost of DES in patients treated

by an ophthalmologist in 6 European countries estimated a total annual healthcare cost between 0.27 and 1.10 million US dollars per country. However, this cost did not take into consideration patients who self-treated their condition or were treated by their primary care physician.[23]

The Medical Expenditure Panel Survey (MEPS) is an annual survey of families and individuals, their medical providers, and employers across the United States. MEPS, which is designed to be representative of the US population, provides the most complete source of data on the cost and use of health care and health insurance coverage.[24] Given that prescription cost information is available through the MEPS data set, we examined recent patterns in dry eye medication expenditures. We aimed to confirm our hypothesis that a substantial increase in expenditures has occurred over the past few years, perhaps in response to the increased public and provider awareness of the condition along with the availability of a new prescription medication.

MATERIALS AND METHODS

Sample

The MEPS is a nationally representative subsample of the National Health Interview Survey, a continuous multipurpose and multistage area probability survey of the US civilian noninstitutionalized population living at addressed dwellings. To have an adequate number of persons in important population subgroups, the MEPS oversampled Blacks and Hispanics in all years and began oversampling of Asians in 2002.[25] The overall MEPS response rate ranged from 66% in 2001 to 58% in 2006. Sampling weights were applied to ensure that the resulting sample was nationally representative of US households and includes adjustment for oversampling of race/ethnic groups and survey nonresponse.

To obtain dry eye medication expenditures, a comprehensive list of available prescription medications, including name brands, generics, and chemical names, for the study period was first generated and used to identify those MEPS participants who used any medication via the MEPS Prescribed Medicines files. The Prescribed Medicines files contained comprehensive information on medications used by MEPS participants.[25] From this list, 2 medications used in the setting of DES were identified: cyclosporine emulsion 0.05%, used to treat aqueous tear deficiency, and sulfacetamide sodium–prednisolone acetate ophthalmic suspension, USP 10%/0.2% (Blephamide), used to treat lipid tear deficiency (blepharitis), among other conditions.

Data from MEPS 2007 were available but were not included in this analysis because the methodology in editing the pharmacy data was changed. Comparison of prescription drug spending before and after 2007 was therefore not recommended by the Agency for Healthcare Research and Quality.[26] MEPS initially had an over-the-counter medication section that collected details about nonprescription medication purchases; however, this section was omitted from the questionnaire beginning in 2002.[27] Because we were interested in dry eye medication costs in the years since the launch of cyclosporine emulsion, we were unable to include over-the-counter medications in our analysis. For the study period, 147 unique participants aged 18 years or older were found to have used sulfacetamide sodium–prednisolone acetate ophthalmic suspension and/or cyclosporine emulsion and were included in the analysis. Expenditure of these medications for each participant over 2-year intervals was analyzed. The data were adjusted for survey design, and the expenditure was adjusted for inflation using 2009 inflation index.

Demographic Data

Demographic and insurance information of the qualified participants was obtained from the MEPS Full-Year Consolidated Data Files. Demographic data collected included gender, age, race (white, black, other/multiple), ethnicity (Hispanic, non-Hispanic), health insurance status (private, public only, and uninsured), and education level (less than high school, high school, greater than high school). Family income, measured as a percentage, was calculated by dividing total family income by the applicable poverty line (based on family size and composition). The resulting percentages were grouped into 3 categories: low income/poverty (less than 200%), middle income (200% to less than 400%), and high income (400% or more).

Statistical Analyses

All statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC) and SUDAAN 10 (RTI International, Triangle, NC) statistical packages. To account for complex survey design of the MEPS data, analyses were completed with adjustments for sample weights and design effects. We conducted descriptive analyses to evaluate patterns in dry eye medication expenses per person over a 2-year interval. *T* tests were performed to compare average medication expenditure across different demographic groups. A multivariate linear regression was performed to study demographic variables that predict high dry eye medication expense. The University of Miami Institutional Review Board reviewed and approved this study, which was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

More patients used prescription dry eye medications in 2005 to 2006 (n = 86) compared with the previous 4 years (n = 29 and 32 for 2001–2002 and 2003–2004, respectively), and the total number of prescriptions filled increased with each year (Fig. 1). The cost associated with dry eye prescription medications also increased between 2001 and 2006, with a mean expenditure per patient of $55 in 2001 to 2002, $137 in 2003 to 2004, and $299 in 2005 to 2006 (Fig. 2). The introduction of topical cyclosporine significantly affected both the number of prescriptions filled and the dry eye expenditures because after its introduction, 68% of prescriptions and 80% of expenditures were related to cyclosporine emulsion in 2003 to 2004 and 84% of prescriptions and 92% of expenditures were related to cyclosporine emulsion in 2005 to 2006. The mean cost of sulfacetamide sodium–prednisolone acetate ophthalmic suspension increased from $36.27 in 2001

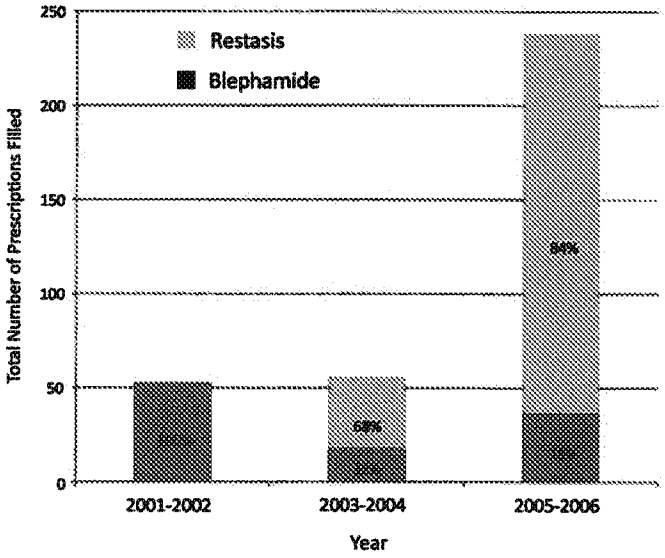

FIGURE 1. Graphic representation of the total number of dry eye prescriptions filled using the MEPS database, 2001 to 2006.

to 2002 to $54.56 in 2003 to 2004 to $64.43 in 2005 to 2006. Likewise, the mean cost of cyclosporine emulsion increased from $98.98 in 2003 to 2004 to $113.06 in 2005 to 2006. The increase in mean dry eye expenditures over the period, therefore, can be explained by both increased medication usage and cost.

Several demographic factors were associated with medication expenditures in the treatment of dry eye. Gender had a significant effect, with mean spending for women being double that for men ($244 vs. $122, $P < 0.0001$) (Table 1, Fig. 2). Similarly, spending for non-Hispanics was double that for the Hispanic population ($228 vs. $106, $P < 0.0001$).

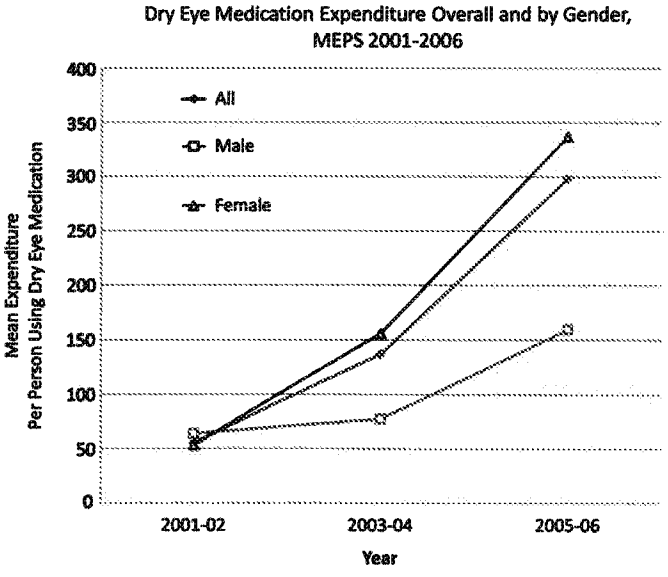

FIGURE 2. Graphic representation of mean dry eye medication expenditures per patient (overall and by gender) using the MEPS database, 2001 to 2006.

Level of education was also an important factor, with individuals with more than a high school education spending more than those with less than a high school education ($250 vs. $100, $P < 0.0001$). Race, age, and income status were not found to significantly affect dry eye medication expenditures in our analysis.

In a multivariable linear regression analysis considering all demographic factors, gender and education remained significant predictors of dry eye medication expenditures. Female gender was associated with a $159 higher mean expenditure compared with male gender ($P = 0.0004$). Greater than high school education was associated with a $145 higher mean expenditure compared with less than a high school education ($P = 0.0016$). Although not significant in our univariable analysis, with adjustment for all other covariates, those in the 65 and older age group spent $107 more on dry eye medications than those in the 45- to 64-year-old group ($P = 0.04$).

DISCUSSION

In this nationally representative study of patterns in prescription dry eye medication expenditures from 2001 to 2006, we found that the number of patients treated with prescription dry eye medications and their associated expenditures increased between these years. This finding was strongly driven by the introduction of cyclosporine emulsion in 2003. Considering demographic factors, female gender, non-Hispanic ethnicity, and a greater than high school education were factors significantly associated with a higher mean yearly expenditure for DES in our univariate models.

Although studies have suggested that the economic implications of DES are substantial,[28] limited data are available to support this statement. Fiscella et al[22] analyzed claims data from a proprietary research database containing pharmacy claims data on over 13 million individuals. They identified 9065 subjects that had one or more prescriptions filled for topical cyclosporine emulsion between January 1, 2004, and December 31, 2005. The mean yearly prescription cost by the health insurance plans was $336, and the mean out-of-pocket prescription cost for the patient was $98. This compares favorably with our findings because the cost analysis above includes both patient and insurance expenditures combined.

Putting these numbers in the context of other chronic ocular and nonocular diseases, a recent MEPS study found that patients with glaucoma spent a mean of $556 per year on prescription glaucoma medications in 2006 (adjusted for inflation using 2009 inflation index).[29] Similarly, another article using the MEPS database found that people with spine problems spent a mean of $397 per year on prescription medications in 2006.[30] The findings in this study suggest that although DES is not a blinding condition, individuals are willing to spend a nontrivial amount of money per year to alleviate the discomfort associated with this disorder. It is also important to note that the expenditures presented in this study do not incorporate the costs of nonprescription medications and doctor's visits and therefore the total amount of money spent on the disease is likely to be significantly higher.

We found that several demographic factors affected the expenditures of dry eye medications, including gender, ethnicity,

TABLE 1. Mean and Standard Error Cost (in Dollars) Per Prescription of Dry Eye Medications by Demographic Factors, 2001 to 2006 MEPS Data

Characteristics	N	Mean	SE	P
All	147	217.31	23.41	—
Sex				
Male	34	122.24	6.87	—
Female	113	244.30	24.35	**<0.0001**
Race				
White	134	220.51	20.63	White vs. Black = 0.07
Black	8	141.94	27.39	White vs. Other = 0.95
Other	5	214.18	95.84	Black vs. Other = 0.47
Ethnicity				
Hispanic	20	106.23	18.89	—
Non-Hispanic	127	227.99	20.78	**<0.0001**
Age group, yr				
18–44	25	192.51	34.40	18–44 vs. 45–64 = 0.78
45–64	53	206.44	27.06	18–44 vs. 65+ = 0.38
65+	69	235.88	34.50	45–64 vs. 65+ = 0.51
Insurance type				
Private insurance	111	225.06	23.01	Private vs. public = 0.57
Public insurance only	29	194.26	45.82	Private vs. uninsured = 0.02*
Uninsured	7	166.56	7.84	Public vs. uninsured = 0.56*
Education				
Less than HS	27	100.18	15.82	<HS vs. HS = 0.05
HS	43	204.54	46.43	**<HS vs. >HS = <0.0001**
Greater than HS	77	250.52	21.78	HS vs. >HS = 0.36
Poverty				
Low income/poverty	33	219.62	37.10	Low vs. middle = 0.14
Middle income	40	168.49	25.46	Low vs. high = 0.64
High income	74	240.57	38.41	Middle vs. high = 0.06

Bold values represent factors significantly associated with increased dry eye expenditures.
*Statistical analyses for the uninsured group are reported but are considered unstable due to small sample size.
HS, high school; SE, standard error.

and education. The presence of gender and ethnic disparities in medical expenditures has been described in other conditions, including mental health[31] and hypertension management.[32] An association between higher expenditures and higher education levels has been reported in systemic lupus erythematosus.[33] Although the etiologies behind these discrepancies are not clear, it is important to recognize the role of demographic factors when considering the myriad determinants of health.

As with all retrospective studies, the study findings must be considered bearing in mind its limitations. One limitation is that information on nonprescription medications was not available in the MEPS database, and we could therefore only estimate costs associated with prescription dry eye medications. As many more patients use over-the-counter medications to treat DES, we failed to include patients with less severe forms of the disease in our analysis. Furthermore, because of changes within MEPS that started in 2007,[26] medication information for this year was not included in the analysis. Another limitation is that the sample size in the present analysis was relatively small, limiting our ability to examine trends in dry eye medication expenditures and in our comparisons in subgroups of interest (eg, the uninsured). Because of the relatively small sample size, it should not be assumed that our analytic sample of dry eye medication users are nationally representative despite the fact that they were obtained from a population-based survey. However, if present patterns continue, there will be a growing number of persons in the MEPS who will use these medications, facilitating future subgroup analyses. Furthermore, both cyclosporine emulsion and sulfacetamide sodium–prednisolone acetate ophthalmic suspension can be used to treat ocular surface disorders other than DES. Because we did not have diagnosis information linked to medication use, it is possible that we included patients treated for ocular surface conditions other than DES in our analysis. Finally, we acknowledge that other medications are used to treat subtypes of DES, including corticosteroids and tetracycline derivates; we chose not to include these in our analysis, given their multiple indications for use. Despite these limitations, there is no other ongoing population-based studies that look specifically at drug medication cost patterns; therefore, the analysis of the MEPS provides us with the best expenditure estimates for newly introduced ocular medications.

In summary, we found a pattern of increased dry eye medication use and expenditure from 2001 to 2006. Women, non-Hispanics, and those with greater than a high school

education had higher expenditures compared with their counterparts. Additional research is necessary to understand the underlying reasons for the difference in dry eye medication expenditures by patient characteristics.

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EXHIBIT C

Dysfunctional Tear Syndrome

A Delphi Approach to Treatment Recommendations

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Purpose: To develop current treatment recommendations for dry eye disease from consensus of expert advice.

Methods: Of 25 preselected international specialists on dry eye, 17 agreed to participate in a modified, 2-round Delphi panel approach. Based on available literature and standards of care, a survey was presented to each panelist. A two-thirds majority was used for consensus building from responses obtained. Treatment algorithms were created. Treatment recommendations for different types and severity levels of dry eye disease were the main outcome.

Results: A new term for dry eye disease was proposed: dysfunctional tear syndrome (DTS). Treatment recommendations were based primarily on patient symptoms and signs. Available diagnostic tests were considered of secondary importance in guiding therapy. Development of algorithms was based on the presence or absence of lid margin disease and disturbances of tear distribution and clearance. Disease severity was considered the most important factor for treatment decision-making and was categorized into 4 levels. Severity was assessed on the basis of tear substitute requirements, symptoms of ocular discomfort, and visual disturbance. Clinical signs present in lids, tear film, conjunctiva, and cornea were also used for categorization of severity. Consensus was reached on treatment algorithms for DTS with and without concurrent lid disease.

Conclusion: Panelist opinion relied on symptoms and signs (not tests) for selection of treatment strategies. Therapy is chosen to match disease severity and presence versus absence of lid margin disease or tear distribution and clearance disturbances.

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Key Words: Delphi panel, dry eye, dysfunctional tear syndrome, eye lubricants, cyclosporine A, punctal plugs, steroids, dry eye therapy, concensus, algorithm

(*Cornea* 2006;25:900–907)

The syndrome known as "dry eye" is highly prevalent, affecting 14% to 33% of the population worldwide,[1–4] depending on the study and definition used. Symptoms related to dry eye are among the leading causes of patient visits to ophthalmologists and optometrists in the United States.[5] However, a stepwise approach to diagnosis and treatment is not well established.

Treatment algorithms are often complicated, especially when multiple therapeutic agents and strategies are available for one single disease and for different stages of the same disease. Dry eye syndrome is particularly challenging, because the diagnostic criteria used vary among studies, there is poor correlation between signs and symptoms, and efficacy criteria are often not uniform. As a result, there is no clear current approach to assign therapeutic recommendations as "first," "second," or "third" line.

Clinical research is usually oriented to assess the efficacy of medications in the treatment of dry eye disease. Reports are based on either comparisons of one medication relative to untreated placebo controls or comparisons between different therapies.[6,7] Categorization of treatment alternatives is usually not implicit in these studies. Strategies combining medications or medications and surgery are usually not clearly discussed in the literature. A panel of experts may be a good method to develop such strategies based on current knowledge, because publication of research may not precede practice. Furthermore, clinical trials are typically performed on highly selected populations with specific interventions that may not reflect the spectrum of disease encountered in usual practice.

Where unanimity of opinion does not exist because of a paucity of scientific evidence and where there is contradictory evidence, consensus methods can be useful. Such methods have been used in developing therapeutic algorithms in other ophthalmic (glaucoma) and nonophthalmic disease states.[8,9]

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The Delphi panel technique was first proposed in 1946 by the RAND Corporation as a resource to collect information from different experts and to prepare a forecast of future technological capabilities. This tool has been expanded to technological,[10] health,[11] and social sciences research.[12] Despite some reasonable criticisms of this technique,[13] the Delphi approach has been used to provide reproducible consensus to create algorithms of treatment.[14,15]

In this study, we proposed to establish expert consensus by using the Delphi approach with an international panel to obtain current treatment recommendations for dry eye syndrome.

MATERIALS AND METHODS

Panelist Selection

The ideal number of panelists expected with this technique is not well defined, with reported ranges from 10 to 1685.[16] No specific inclusion criteria are established, other than the qualification of panelists in the topic of interest. Some authors stress the importance of the diversity of panelists' opinion to obtain a wide base of knowledge.[17]

The following criteria were considered for inclusion of panelists:

1. Active clinicians (ophthalmologists and optometrists)
2. Scientific contributions to clinical research on dry eye syndrome, as reflected by at least 2 of the following: peer-reviewed publications, other forms of written scientific communication, specialty meeting presentations, and membership in special-interest groups focused on dry eye syndrome
3. International representation
4. Proficiency in English language to facilitate interaction
5. Able to respond to sets of questionnaires and available to attend a final meeting at the Wilmer Ophthalmological Institute in Baltimore, MD

The search for panelists' scientific contributions was conducted over available medical databases (Medline, EMBASE) and other major Internet-based search engines (Scirus.com, Google.com, Alltheweb.com). Twenty-five candidates from 3 continents that met the selection criteria were initially contacted.

A contract research organization (Analytica Group, New York, NY) was selected to act as moderator/facilitator for the questionnaire and panel meeting exercise. A 2-round modified Delphi approach was used.[18] A set of dry eye therapy literature was provided to each panel member along with the first-round questionnaire. These studies were selected in part from an ongoing systematic review of the literature on dry eye disease therapy. Three of the panelists suggested additions of some references that they considered valuable. Those citations were also disseminated to the rest of the panelists.

Preparation of Surveys

Questionnaires were based on collected literature, current practice patterns, and clinical experience in dry eye. Topics in the survey were related to pathophysiology, diagnostic tests, criteria used to guide treatment, and therapeutic alternatives.

Nominal variables were assigned binary values to tabulate responses in a spreadsheet (Excel 2002; Microsoft Corp., Redmond, WA) for analysis. Ordinal variables were originated from 5-point Likert scales to categorize the strength of agreement and facilitate the statistical analysis.

Survey questions were based on the use of the current classification of dry eye disease and the available guidelines for the treatment. Diagnostic methods and severity assessment were also surveyed. Panelists were asked to support their multilevel treatment recommendation with a categorical, nominal score of 1 to 3, depending on the level of evidence to sustain their decision:

1. Supported by a clinical trial
2. Supported by published literature of some type
3. Supported by my professional opinion

Finally, determinant factors influencing the treatment decision-making process were stratified semiquantitatively to evaluate the most representative for the selection of therapy.

Survey Deployment

The forms were deployed by electronic mail to the panelists. The information obtained from the surveys was tabulated and organized for presentation at the face-to-face meeting of the Delphi process.

Data Analysis

Descriptive statistics were calculated for the questionnaire data by using StatsDirect 2.3.7 for Windows (StatsDirect, Cheshire, UK).

Consensus

There exists controversy regarding the numbers necessary to obtain consensus. Some authors agree that a simple majority (>50%) is enough to constitute consensus,[19] whereas others propose that more than 80% of panelists should be in agreement to have the recommendation considered as consensual.[20] Degree of consensus has also been quantified statistically using the Cronbach α method, a method for measuring internal agreement.[21] For the purposes of this study, consensus was defined as a two-thirds majority.

Personal Interaction

The meeting was conducted by a facilitator (J.J.D.) with previous experience in consensus-building strategies.[8] Panelists reacted and discussed the data collected from the surveys over an intensive 1-day, 12-hour-long, face-to-face meeting. According to the tabulated initial responses, iterative discussions were conducted toward majority agreement.

RESULTS

Panelists' Response

From the initial selection of 25 candidates who met the inclusion criteria, 17 were able to participate in all stages of the study and therefore were included in the panel. The candidates who refused to join the panel did not have substantive reasons precluding their participation. Most of them declined to participate because of scheduling conflicts. The list of participants is shown in Table 1. All surveys deployed were returned with responses from all of the panelists.

TABLE 1. Experts Who Participated in the Delphi Approach (DTS Study Group)

Panelist Name	City	Country
Dimitri T. Azar, M.D.	Boston, MA	United States
Harminder S. Dua, M.D., Ph.D	Nottingham	England
Milton Hom, O.D.	Azusa, CA	United States
Paul M. Karpecki, O.D.	Overland Park, KS	United States
Peter R. Laibson, M.D.	Philadelphia, PA	United States
Michael A. Lemp, M.D.	Washington, DC	United States
David M. Meisler, M.D.	Cleveland, OH	United States
Juan Murube del Castillo, M.D., Ph.D.	Madrid	Spain
Terrence P. O'Brien, M.D.	Baltimore, MD	United States
Stephen C. Pflugfelder, M.D.	Houston, TX	United States
Maurizio Rolando, M.D.	Genoa	Italy
Oliver D. Schein, M.D., M.P.H.	Baltimore, MD	United States
Berthold Seitz, M.D.	Erlangen	Germany
Scheffer C. Tseng, M.D., Ph.D.	Miami, FL	United States
Gysbert B. van Setten, M.D., Ph.D.	Stockholm	Sweden
Steven E. Wilson, M.D.	Cleveland, OH	United States
Samuel C. Yiu, M.D, Ph.D.	Los Angeles, CA	United States

Conflicts of Interest

Travel expenses of panelists were covered by the contracted company (Analytica Group), which is an independent firm. The Wilmer Eye Institute originated the invitation, and panelists were unaware of any indirect support from pharmaceutical industry to avoid bias in the treatment selection.

Use of Existing Disease/Treatment Guidelines

The majority of panelists (11 of 17) responded that they did not follow any of the available guidelines for the treatment of dry eye syndrome. Three of 17 followed the National Eye Institute guidelines,[22] 1 of 17 followed the American Academy of Ophthalmology Preferred Practice Patterns,[23] 1 of 17 followed the Madrid classification,[24] and 1 of 17 followed a combination of the first 2 guidelines.

When panel members were asked about their opinions regarding the adherence of the ophthalmic community to new, simplified guidelines for the treatment of dry eye, the majority (13 of 17) agreed that they would use them if most recent findings on the disease were included. Those who responded that they would not use them (4 of 17), based their response on the low sensitivity and specificity of the available tests for the diagnosis of dry eye and the variability of the clinical presentation in different patients.

Diagnostic Tests for Dry Eye

When panelists were surveyed before the meeting on diagnostic measures used to detect dry eye, the most frequently cited tests were slit-lamp examination and fluorescein staining (100% of panelists). Tear breakup time and medical history were also frequently used (both in 94%). Schirmer test with anesthesia (71%) and without anesthesia (65%) were less frequently used, as well as rose bengal staining (65%). A combination of different tests was typically preferred in an effort to improve the specificity and sensitivity (Table 2).

TABLE 2. Most Commonly Used Diagnostic Tests Reported by Panelists for Evaluating a Patient With Probable Dry Eye

Diagnostic Tests	Respondents Regularly Using Them (%)
Fluorescein staining	100
Tear breakup time	94
Schirmer test	71
Rose bengal staining	65
Corneal topography	41
Impression cytology	24
Tear fluorescein clearance	24
Ocular Surface Disease Index Questionnaire	18
NEIVFQ-25*	6
Tear osmolarity	6
Conjunctival biopsy	6

*NEIVFQ-25: National Eye Institute Vision Function Questionnaire-25.

Classification of Dry Eye Disease

More than one half of the respondents felt that the current classification of aqueous-deficient versus evaporative dry eye failed to incorporate inflammatory mechanisms and drew a sharp distinction between disorders where there is significant overlap.[25,26] Furthermore, the historical distinction between Sjögren keratoconjunctivitis sicca (KCS) as representing an autoimmune disorder as opposed to non-Sjögren KCS failed to reflect the evidence that both conditions may share an underlying immune-mediated inflammation. The majority of experts did not consider this useful for establishing a treatment scheme for the ocular disease (12 of 17). The panelists considered the disease severity and the effect of medications on symptoms and signs as the 2 most relevant factors to consider when selecting the adequate therapy for dry eye (Table 3).

Face-to-Face Meeting

At the face-to-face meeting, panel members made comments on the term "dry eye" classically used to name the disease. On the basis of the known pathophysiology, symptoms, and clinical presentation, all panelists agreed that this term did not necessarily reflect the events occurring in the eye. Specifically, all patients with this condition do not necessarily

TABLE 3. Most Relevant Factors Influencing Treatment Decision Making

Factor Considered	Mean Score (Standard Deviation)
Severity of the disease	1.47 (0.72)
Effect of the treatment	1.79 (0.77)
Etiology of the disease	2.08 (1.07)
Diagnosis of Sjögren's syndrome	2.20 (1.05)
Use of artificial tears	3.07 (1.53)
Costs of treatment	3.80 (1.17)
Access to reimbursement	3.92 (1.10)

0 = most relevant; 5 = least relevant.

suffer from reduced tear volume but rather may have abnormalities of tear film composition that include the presence of proinflammatory cytokines.[25–27] The panelists unanimously recommended dysfunctional tear syndrome (DTS) as a more appropriate term for this disease in future references. This term has been incorporated in the rest of this report in lieu of dry eye disease.

Underlying Pathophysiology and Diagnostic Testing

There was consensus that most cases of DTS have an inflammatory basis that either triggers or maintains the condition. However, panelists also agreed on the difficulty in clearly identifying inflammation in most patients. The panel therefore agreed to subclassify the disease as either DTS with clinically apparent inflammation or DTS without clinically evident inflammation.

After discussion at the meeting, the panelists were in agreement that commonly available clinical diagnostic tests did not correlate with symptoms, should not be used in isolation to establish the diagnosis of DTS, and were of minimal value in the assessment of disease severity.

Creation of Therapeutic Algorithms for DTS

First, the panel recommended that patients with DTS should be classified into 1 of 3 major clinical categories at the time of the initial examination: patients with lid margin disease, patients without lid margin disease, and patients with altered tear distribution and clearance.

The panel agreed that the second group, patients who do not have coexistent lid margin disease, is the most common form of presentation of DTS. Within each of these 3 categories, the panel listed the main subsets or specific disease entities or, in the case of DTS without lid margin disease, the patients were divided by severity (Fig. 1). Second, the panel agreed that the assessment of DTS severity is important to guiding therapy, especially in that subset of DTS patients without lid margin disease. The panel reached consensus that the level of severity should be based primarily on symptoms and clinical signs.

The panel members agreed that diagnostic tests are secondary considerations in determining disease severity. The value of diagnostic tests was considered to be in confirming clinical assessment. Again, many of the available tests were deemed not useful for the diagnosis, staging, or evaluating response to therapy in DTS.

Panelists agreed on 3 particularly relevant symptoms and historical elements to be considered in DTS: ocular discomfort, tear substitute requirements, and visual disturbances. In ocular discomfort, a variety of symptoms including itch, scratch, burn, foreign body sensation, and/or photophobia may be present. Depending on the frequency and impact on the quality of life of these elements, symptoms could be categorized as either mild to moderate or severe. The relevant clinical signs to be considered in the evaluation of DTS patients are summarized in Table 4. The panel suggested evaluating the presence of these clinical features to assign a severity level fluctuating from mild to severe.

To create a categorization of the severity of the disease, a scoring system was proposed. Basically, patients were aggregated into 1 of 4 levels of severity according to the signs and symptoms involved (Table 5). The severity of disease indicated the appropriate range of therapeutic options available for the patient, because the panelists agreed that certain therapies were most appropriately reserved for patients with more severe DTS.

Treatment Algorithm for Patients With Lid Margin Disease

The proposed treatment algorithm for these individuals began with division of patients according to the site (anterior vs. posterior) of the lid pathology (Fig. 2). Anterior lid margin disease is treated with lid hygiene and antibacterial therapy, whereas posterior lid margin disease is treated initially with

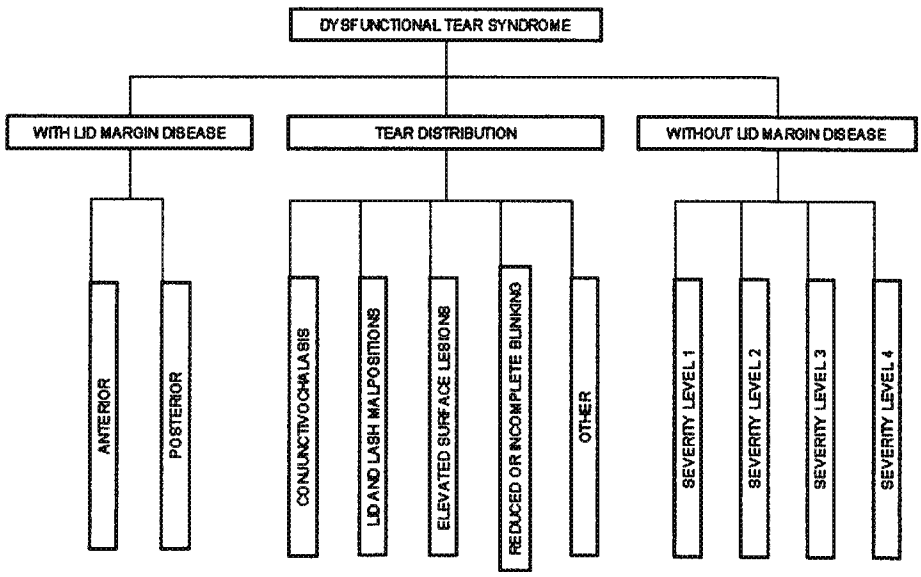

FIGURE 1. Algorithm of the 3 major subsets found in DTS. Each subset should be treated separately, because treatment modality varies according to this separation.

TABLE 4. Clinical Signs in DTS to Consider in Severity Assessment

Lids	Tear Film	Conjunctiva	Cornea	Vision
Telangiectasia	Meniscus	Luster	Punctate changes	Blur
Hyperemia	Foam	Hyperemia	Erosions (micro, macro)	Fluctuations
Scales, crusts	Mucus	Wrinkles	Filaments	
Lash loss or	Debris	Staining	Ulceration	
abnormalities	Oil excess	Symblepharon	Vascularization	
Inspissation		Cicatrization	Scarring	
Meibomian gland disease			Keratinization	
Anatomical abnormalities				

warm massage, with addition of oral tetracyclines and topical corticosteroids, if necessary.

Treatment Algorithm for DTS Patients With Primary Tear Distribution and Clearance Abnormalities

The panel considered that there were patients in whom the even distribution of tears across the ocular surface is impaired, typically related to an anatomic abnormality or to abnormal lid function (Fig. 3). The recommended therapeutic approach to these patients varied in accordance with the specific underlying problem, which is summarized in Figure 3.

Treatment Algorithm for DTS Patients Without Lid Margin Disease

Patients with mild disease are best managed with patient education about the disease and strategies for minimizing its impact, preserved artificial tears, modification as appropriate of systemic medications that might contribute to the condition, and perhaps changes in the home or work environment to alleviate the symptoms (Fig. 4).

In patients in whom the disease state is moderate or severe, the panelists agreed that the more frequent use of tears mandated a switch to unpreserved lubricants, with tears during the day, ointment at night, and consideration of progression to a gel formulation during the day if relief was not adequate with tears. In the absence of signs, the panel recommended lubrication, with frequency determined by the clinical response.

In the presence of signs (eg, moderate corneal staining, filaments), the panel agreed on a stepwise introduction of additional therapies. The panelists noted that patients with DTS may have an inflammatory component, which may or may not be clinically evident. In addition to the use of unpreserved tears, the panel recommended a course of topical corticosteroids and/or cyclosporine A to suppress inflammation.

In patients who fail to respond adequately to lubricants and topical immunomodulators, a course of oral tetracycline therapy was recommended, as well as punctal occlusion with

TABLE 5. Levels of Severity of DTS Without Lid Margin Disease According to Symptoms and Signs

Severity*	Patient Profiles
Level 1	• Mild to moderate symptoms and no signs
	• Mild to moderate conjunctival signs
Level 2	• Moderate to severe symptoms
	• Tear film signs
	• Mild corneal punctate staining
	• Conjunctival staining
	• Visual signs
Level 3	• Severe symptoms
	• Marked corneal punctate staining
	• Central corneal staining
	• Filamentary keratitis
Level 4	• Severe symptoms
	• Severe corneal staining, erosions
	• Conjunctival scarring

*At least one sign and one symptom of each category should be present to qualify for the corresponding level assignment.

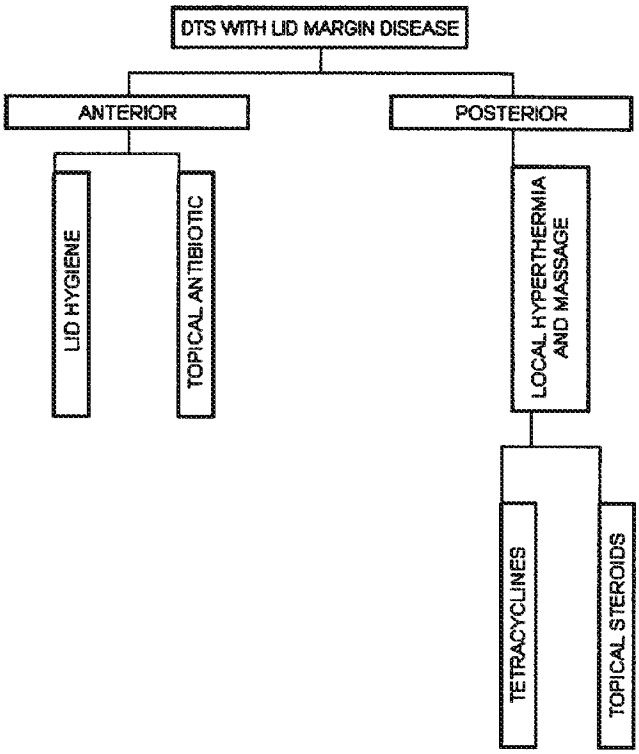

FIGURE 2. Algorithm on treatment recommendations for DTS with lid margin disease.

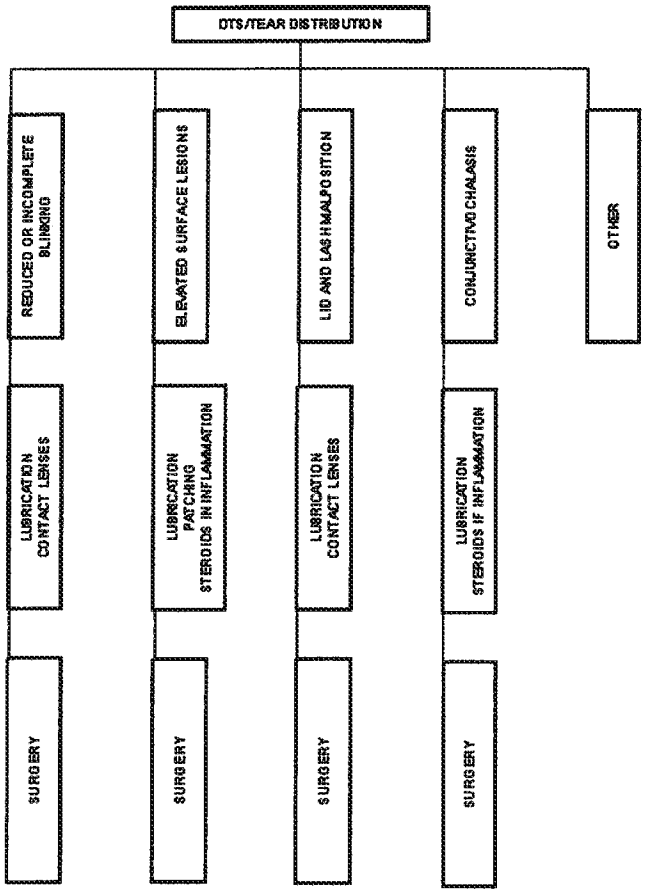

FIGURE 3. Algorithm on treatment recommendations for DTS with abnormal tear distribution.

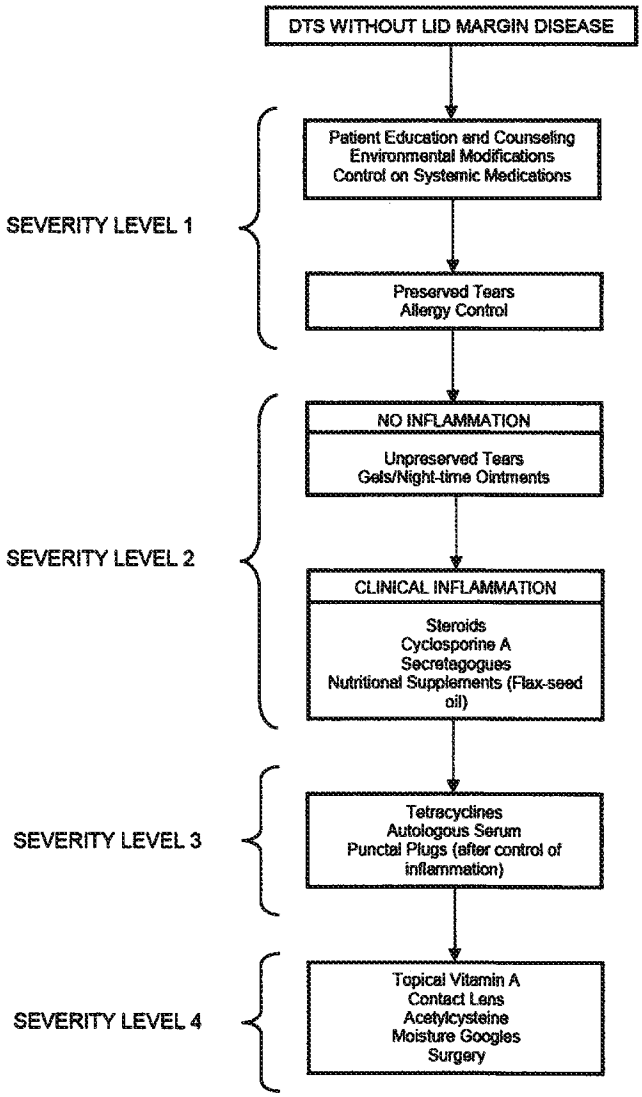

FIGURE 4. Algorithm on treatment recommendations for DTS without lid margin disease according to severity.

plugs. Because of the possible presence of non–clinically apparent inflammation, punctal plugs could result in retention of proinflammatory tear components on the ocular surface and may enhance damage to the ocular surface, accelerate the disease process, and produce greater patient discomfort. Therefore, the panel agreed that it is important to treat the inflammatory condition before blockage of tear drainage with punctal plugs.

Patients with severe disease who are not adequately controlled after the above therapeutic interventions may benefit from more advanced interventions. These would include systemic immunomodulators for the control of severe inflammation, topical acetylcysteine for filament formation caused by mucin accumulation, moisture goggles to reduce tear evaporation, and surgery (including punctal cautery) to reduce tear drainage. Patients with Sjögren syndrome would fit within this category.

DISCUSSION

Some researchers have stressed the use of Delphi panels in clinical research, despite some flaws in terms of reproducibility and other confounding factors that may adversely influence the results.[28,29] Delphi approach is not necessarily "evidence-based": Good evidence may exist contradicting a particular consensus; or conversely, evidence for a particular consensus may be absent, because it has not been adequately studied. Especially for areas where there is little or no good evidence in the literature, the process relies on the opinion of the participating panelists, potentially tapping into collective error.[30] Moreover, consensus is subject to particular interpretation of evidence and personal experience, which may affect reproducibility.[14] Nonetheless, this process has lately become popular to delineate guidelines of treatment of various disorders.[30–33]

Bias of panelists' selection may inevitably occur as a result of the inclusion criteria chosen. It is a common observation that highly published authors tend to have some

form of commercial support from pharmaceutical industry. Nine of 17 panelists disclosed a past or present relationship as a speaker/consultant/research funds recipient from companies having products for the treatment of DTS.

The success of a Delphi panel is based largely on the ability of the facilitator to maintain balanced participation of panelists.[32] One of the major challenges in such panels is to avoid the inadvertent control of one or more leaders over the discussion.[30] The facilitator in our study was a person with previous experience in consensus panels. He had the ability to encourage homogeneous participation of panel members. The facilitator focused on the varied responses previously given by panelists in the survey to avoid discussions over a single topic/therapeutic approach raised by individual participants during the meeting. Inevitable discrepancies were observed during the DTS panel meeting; however, consensual agreement among panelists was finally achieved.

We believe that one significant consequence of the panel meeting was the recommendation for a change from the term dry eye, frequently used to describe the condition, to the term dysfunctional tear syndrome. Panelists unanimously agreed that the label dry eye reflects neither patient symptoms nor necessarily the pathogenic mechanism of the disease. Panel members also agreed that diagnosing patients with dry eye may be misleading to both colleagues and patients. Patients may be confused when excess tearing is their primary complaint and are diagnosed as having dry eye. Even more confusing for patients is their subsequent treatment with anti-inflammatory agents or antibiotics. For these reasons, the term DTS was coined, because the panel felt that this term was sufficiently broad to encompass the myriad of etiologies while still representing a common denominator among them.

There was consensus that severity of disease should be the primary determinant for the therapeutic strategy chosen. In addition, observation of the patient response to initial therapy was deemed as an important indicator of disease severity and further treatment selection. The failure on improvement using medications in one level assigns the patient to additional therapy in the immediate superior severity level. The available diagnostic tests were not considered important in the assessment of disease severity and therefore were not included in the classification. However, this should not underestimate the value of these tests in the diagnosis of DTS, because they were regularly used by panelists to confirm the presence of the disease.

The task of creating guidelines for DTS is complex, because practitioners encountering DTS are faced with a multifactorial disorder with several pathophysiological events that may require a variety of customized therapeutic schemes. Moreover, significant overlapping between the categories selected by the panel is also likely. The summary treatment recommendations (Table 6) relating severity of disease with clinical symptoms and signs created by the panel may serve as a useful guide. It is recognized that individual patient characteristics may require deviation from recommended treatment, but panelists were clear that the ideal therapy for DTS is often achieved with a combination of interventions. Assignment of levels of severity may work only as a stepwise guide to approaching the best combination of medications to avoid symptoms. It is important to stress that patients may present with signs belonging to different categories of DTS (ie, a patient may have DTS with lid margin disease and exhibit tear distribution problems).

Those particular patients should be treated according to recommendations for both categories to succeed in controlling their symptoms and signs. Published guidelines in other disease areas have proven useful to general practitioners to approach a complex disease like DTS.[14,15,17] Some examples using the Delphi technique have been reported in esophageal cancer management,[11] systemic hypertension treatment algorithms,[15] and acute diarrhea management in children.[30] In this study, the Delphi approach was used to gain a practical approach to the diagnosis and treatment of DTS, as opposed to an extensive evaluation of available diagnostic methods or pathophysiology mechanisms, already well documented in the literature[34–38] (Table 7).

TABLE 6. Treatment Recommendations for DTS on the Basis of Level of Severity

DTS Severity	Treatment Recommendations	
Level 1	• No treatment	• Use of hypoallergenic products
	• Preserved tears	• Water intake
	• Environmental management	• Psychological support
	• Allergy drops	• Avoidance of drugs contributing to dry eye
Level 2	• Unpreserved tears	• Secretagogues
	• Gels	• Topical steroids
	• Ointments	• Topical cyclosporine A
	• Nutritional support (flaxseed/fatty acids)	
Level 3	• Tetracyclines	
	• Punctal plugs	
Level 4	• Surgery	• Punctal cautery
	• Systemic anti-inflammatory therapy	• Acetylcysteine
	• Oral cyclosporine	• Contact lenses
	• Moisture goggles	

TABLE 7. Advantages of the Proposed Recommendations by the Delphi Panel

- Proposes a new terminology for dry eye disease (dysfunctional tear syndrome) from recent pathophysiologic findings
- Includes novel therapeutic options in the market
- Provides simplified therapeutic recommendations in a stepwise approach
- Patients without lid margin disease/tear distribution problems are assigned to 4 severity levels
- Severity levels are categorized according to patient's signs and symptoms, not tests
- Therapeutic options are oriented by severity levels
- Easier approach for general eye care practitioners

All guidelines are limited by the future development of new treatments and by new insights that future research will bring. We therefore regard these guidelines as a platform onto which future updates may be added.

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EXHIBIT D

Management and Therapy of Dry Eye Disease:
Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **The members of the Management and Therapy Subcommittee assessed current dry eye therapies. Each member wrote a succinct evidence-based review on an assigned aspect of the topic, and the final report was written after review by and with consensus of all subcommittee members and the entire Dry Eye WorkShop membership. In addition to its own review of the literature, the Subcommittee reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on Dry Eye. The Subcommittee favored the approach taken by the ITF, whose recommended treatments were based on level of disease severity. The recommendations of the Subcommittee are based on a modification of the ITF severity grading scheme, and suggested treatments were chosen from a menu of therapies for which evidence of therapeutic effect had been presented.**

KEYWORDS **DEWS, dry eye disease, Dry Eye WorkShop, management, therapy**

I. INTRODUCTION

This report summarizes the management and therapeutic options for treating dry eye disease. The level of evidence for supporting data from the literature is evaluated according to the modified American Academy of Ophthalmology Preferred Practices guidelines (Table 1).

II. GOALS OF THE MANAGEMENT AND THERAPY SUBCOMMITTEE

Goals of this committee were to identify appropriate therapeutic methods for the management of dry eye disease and recommend a sequence or strategy for their application, based on evidence-based review of the literature.

The quality of the evidence in the literature was graded according to a modification of the scheme used in the American Academy of Ophthalmology Preferred Practice Patterns series. When possible, peer-reviewed full publications, not abstracts, were used. The report was reviewed

Table 1. Evidence grading scheme

Clinical Studies
Level 1. Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches.
Level 2. Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more center, or a well-designed study accessible to more rigorous statistical analysis.
Level 3. Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion.
Basic Science Studies
Level 1. Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal.
Level 2. Preliminary or limited published study.
Level 3. Meeting abstracts or unpublished presentations.

This evidence grading scheme is based on that used in the American Academy of Ophthalmology Preferred Practice Pattern series.

Accepted for publication January 2007.

Management and Therapy Subcommittee members: **Stephen C. Pflugfelder, MD (Chair)**; Gerd Geerling, MD; Shigero Kinoshita, MD; Michael A. Lemp, MD; James McCulley, MD; Daniel Nelson, MD; Gary N. Novack, PhD; Jun Shimazaki, MD; Clive Wilson, PhD.

Proprietary interests of Subcommittee members are disclosed on pages 202 and 204.

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