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NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 12/06/2013

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

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1658	

DATE MAILED: 12/06/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/06/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 12/06/2013
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

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13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

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nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/06/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1658	514-020500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. 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 12 minutes 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1658	

DATE MAILED: 12/06/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notices of Allowance and Fee(s) Due mailed between October 1, 2013 and December 31, 2013

(Addendum to PTOL-85)

If the "Notice of Allowance and Fee(s) Due" has a mailing date on or after October 1, 2013 and before January 1, 2014, the following information is applicable to this application.

If the issue fee is being timely paid on or after January 1, 2014, the amount due is the issue fee and publication fee in effect January 1, 2014. On January 1, 2014, the issue fees set forth in 37 CFR 1.18 decrease significantly and the publication fee set forth in 37 CFR 1.18(d)(1) decreases to $0.

If an issue fee or publication fee has been previously paid in this application, applicant is not entitled to a refund of the difference between the amount paid and the amount in effect on January 1, 2014.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/967,179	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 L. WINE*. (4)_____.

Date of Interview: *17 October 2013*.

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: *37,54 and 60*.

Identification of prior art discussed: *US 5,474,979 and US 6 984,623*.

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: Authorization for communication under MPEP 502.03 was filed on 10/1/2013 by Applicant's representative.Courtesy copies of the OA and response were exchanged via email by Examiner (10/7/2013, see attachment of the email communication. Examiner emailed a courtesy copy of the OA on 10/7/2013). Applicant's representative emailed a courtesy copy of the response to the OA on 10/14/2013. The exchanged copies were identical to the OA and response of record, therefore, for the sake of clarity they have not been herein included) and Applicant's representative. Applicant's representative contacted Examiner on 10/17-18/2013,10/23/2013, 10/28/2013 and 10/30/2013 and 11/1/2013 to inquire about the application, provide updates regarding the status of the application and filings and/or discuss any potential questions and related applications. Examiner provided updates regarding the status of the examination as requested. On 10/18/2013, Examiner contacted Applicant's representative to discuss the affidavits EXHIBIT 1 and 2 were discussed specifically with regards to the excipients used in phase2 and phase3 of the clinical trials described therein, Applicant's representative indicated that the excipients were identical in these 2 phases and that this was also set forth in the affidavits, which was confirmed by Examiner (e.g., page 2, paragraph 8 of EXHIBIT 1). On 10/23/2013, Applicant's representative along with Maysa Attar contacted Examiner to discuss whether any outstanding questions remained from the examination of the courtesy copies of the affidavits. Examiner did not have any further questions and indicated that she would act on the case when the official papers were filed. Laura Wine contacted Examiner on 10/28/2013 indicating that the response had been filed on 10/23/2013. During the final search Examiner found a potential 103(a) reference (US 6 984,623, Table 5) on 11/4/2013. Applicant's representative filed a statement of common ownership for US 6984623 (corresponding to US 2005/0014691) and the instant application. The statement is deemed sufficient to obviate an obviousness rejection over US 6,984,623. Furthermore, in telephonic conversations on 11/8/2013, 11/15/2013 and 11/20/2013 Applicant's representative inquired about the status of the instant application. Examiner indicated that she would contact Applicant's representative whenever examination proceeded. In a telephonic conversation on 11/25/2013 Examiner further discussed and requested a TD for 13/649,287 in order to obviate potential ODP rejections. The TD was filed and approved on 11/25/2013.

Notice of Allowability	Application No. 13/967,179	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1658	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/07/2013, 10/14/2013 and 11/07/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *37-57, 59-61*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20131120* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

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

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. This Office Action is in response to the replies received on 10/07/2013, 10/14/2013 and 11/07/2013.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Status of the claims

3. Claims 37-61 were pending in the application. Claims 37, 44, 47, 49, 50, 51, 52, 53, 54, 57, 60 have now been amended. Claim 58 has been cancelled. Claims 37-57, 58-61 are presented for examination on the merits.

Declarations under 37 CFR 1.132

4. The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 3 comprising EXHIBITS A, B and C) has been carefully considered, however it is deemed insufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: "Objective evidence of nonobviousness including commercial success must be commensurate in scope with the claims. *In re Tiffin*, 448 F.2d 791, 171 USPQ 294 (CCPA 1971) (evidence showing **commercial** success of thermoplastic foam "cups" used in vending machines was not commensurate in scope with claims directed to thermoplastic foam "containers" broadly). In order to be commensurate * > in < scope with the claims, the **commercial** success must be due to claimed features, and not due to unclaimed

features. *Joy Technologies Inc. v. Manbeck,* 751 F. Supp. 225, 229, 17 USPQ2d 1257, 1260 (D.D.C. 1990), *aff'd*, 959 F.2d 226, 228, 22 USPQ2d 1153, 1156 (Fed. Cir. 1992) (Features responsible for **commercial** success were recited only in allowed dependent claims, and therefore the evidence of **commercial** success was not commensurate in scope with the broad claims at issue." (MPEP 716.03). In the instant case, compositions comprising any of the previously discussed embodiments of Ding et al. (i.e., Examples D, E) were not commercially available nor were compared in the declaration. Therefore, Examiner cannot ascertain whether the commercial success of the claimed composition was due to the claimed features which are distinct from those embodiments in Ding et al. or other factors such as the fact that the composition was the only composition for treating dry eyes FDA approved and thus, commercially available for sale to the public (see, e.g. EXHIBIT 4, pages 4-5, paragraphs 8-9).

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 4, comprising EXHIBITS A-O) is insufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: "Establishing **long-felt need** requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of **long-felt need** and the failure of others to the issue of obviousness depends on several factors: (I) First, the need must have been a persistent one that was recognized by those of ordinary skill in the art; (II) Second, the **long-felt need** must not have been satisfied by another before the invention by applicant and (III) Third, the invention must in fact satisfy the long-felt need (MPEP 716.04). In the instant case, with

respect to (II), the prior art abundantly provides for methods of treating dry eye disease with cyclosporin and other active agents, e.g., Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013), Kawashima et al. (US 6,582,718, cited in the IDS dated 9/11/2013), Ding et al. (US 5,981,607, cited in the IDS dated 9/11/2013) and Benita et al. (US 6,656,460, cited in the IDS dated 9/12/2013). Therefore, (II) has not been met and the arguments regarding long-felt need have not been deemed persuasive.

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 1, comprising EXHIBITS A-F) is deemed sufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: After carefully reviewing exhibits A-F, which compare the instantly claimed embodiment having 0.05%/1.25% castor oil with embodiments E and F of Ding et al. (0.10%/1.25% castor oil and 0.05/.625% cyclosporin/castor oil ratios), Examiner is persuaded that, unexpectedly, the claimed formulation (0.05% cyclosporin A/1.25% castor oil) demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test score in the first study of 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 represents a comparison of the subpopulation of Phase 2 patients using compositions with the same reductions in tear production (5 mm/5 min) as those enrolled in the Phase 3 studies. EXHIBIT 1 at paragraph 8. All of the cyclosporin A-containing formulations as well as the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate, 0.05% Pemulen, sodium hydroxide, and water (see paragraph 6, page 2 of EXHIBIT 1).

Exhibits E and F also illustrate that the claimed formulations comprising 0.05% cyclosporin A/1.25% castor oil 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). The excipients were the same in the compared compositions. Given that the compositions comprise the same amount of active agent (0.05 % cyclosporin A) as Ding 1E, the improvements are surprising, unexpected and commensurate in scope with the claimed invention.

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 2, comprising EXHIBITS A-D) is deemed sufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: EXHIBITS A-D were carefully reviewed. As described in paragraph 7 of the EXHIBIT 2, the chart in EXHIBIT B 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 et al. 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the claimed formulation) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D). According to Dr. Attar, this data teaches that 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. EXHIBIT A, paragraph 8. Therefore it would be unexpected that the composition with lower uptake in cornea and conjunctiva would have significantly improved activity.

Taking the results of the studies and data presented in the EXHIBITS 1 and 2 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 Declarations in EXHIBIT 1 and EXHIBIT 2, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed formulations, including 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 et al., including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D) which are the closest prior art formulations. The unexpected results are commensurate in scope with the claims (MPEP 716.02(d)).

Thus, the obviousness rejection in view of Ding et al. is herein withdrawn.

Double Patenting

5. The ODP rejection over Ding et al. is herein withdrawn for the reasons set forth in section 4 above.

Statutory double patenting rejection

6. The statutory double patenting rejection over 13/961,818 is withdrawn in view of Applicants' amendments to the instant claims and those of the cited application.

Terminal disclaimers

7. Terminal disclaimers for 13/961,168; 13/967,163; 13/961,828; 13/967,189; 13/961,808; 13/961,818, 13/61,835 were received and accepted on 10/7/2013. Therefore, the ODP rejections of record and potential ODP for 13/961,818 -as now amended- have been withdrawn.

Further, upon reconsideration, Examiner also requested a TD for 13/649,287 in a further telephonic communication on 11/25/2013. This TD was received and accepted on 11/25/2013

Examiner contacted Applicant's representative on 11/7/2013 and discussed US 6,984,628. In order to obviate a potential obviousness rejection over US 6,984,628 (corresponding to US 2005/0014691, cited in the IDS dated 9/11/2013), Applicant's representative filed a statement on 11/7/2013 that the '691 Publication should be disqualified under 35 U.S.C. 103(c) because the present application and the '691 publication, at the time the invention of the present application was made, were owned by or subject to an obligation of assignment to Allergan, Inc. The statement was carefully considered and deemed persuasive.

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 11/2013

Docket No. 17618CON5B (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 13/967,179	Group Art Unit: 1658
Filed: August 14, 2013	Confirmation No. 8654
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 treating dry eye disease, the method comprising topically administering to the eye of ~~the~~ a 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 treating dry eye disease.

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 treating dry eye syndrome~~, 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 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 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 ~~include~~ are side effects.

54. (**Currently Amended**) A method of reducing side effects in a human ~~suffering from~~ being treated for dry eye syndrome, the method comprising the step of 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;

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 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~~ for treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

58. (Canceled)

59. (Previously Presented) The method of Claim 54, wherein the emulsion is effective in treating dry eye disease.

60. (**Currently Amended**) A method of treating dry eye disease, 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;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water;

wherein the emulsion is effective in treating dry eye disease.

61. (Previously Presented) The method of Claim 60, 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 37-61. Claim 58 is newly cancelled. Claims 37, 44, 47, 49-54, 57, and 60 have been amended. Thus, Claims 37-57 and 59-61 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 37-61 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.

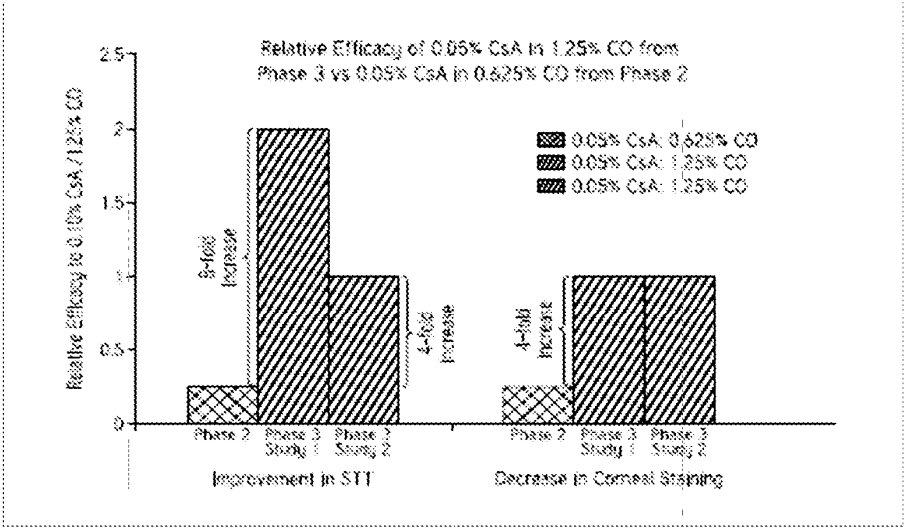
As described by Dr. Schiffman in paragraphs 17-20 of Schiffman Declaration 1 and as seen in Exhibits E and F to Schiffman Declaration 1, surprisingly, the claimed methods demonstrated an *8-fold* increase in relative efficacy for the Schirmer Tear Test ("STT") score in the first study of Allergan's Phase 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*)

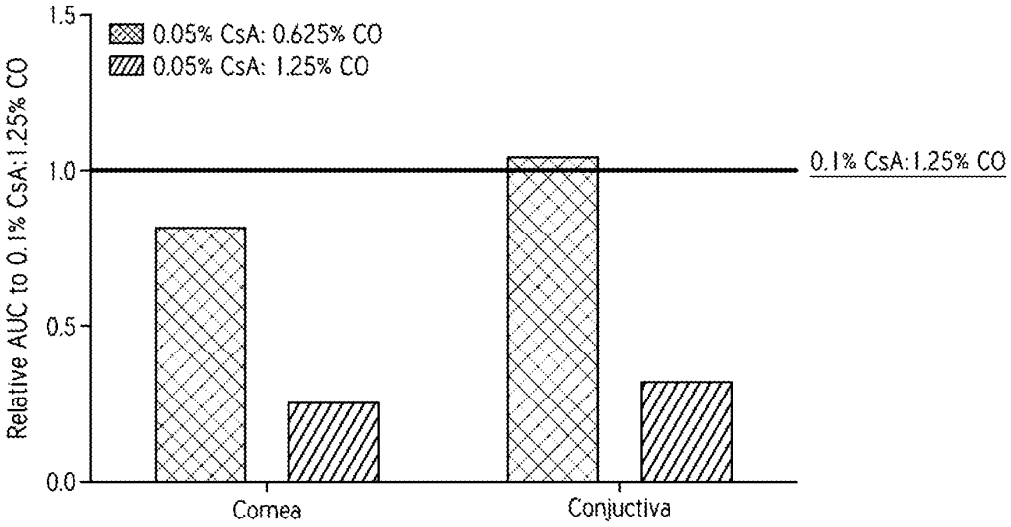
*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

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 60). 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 37-61 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 37-61 in view of claims 1-8 of Ding.

Provisional Obviousness-Type Double Patenting Rejection

Claims 37-61 were rejected for provisional non-statutory obvious-type double patenting in view of claims 37-60 of copending U.S. Patent Application No. 13/967,168, claims 37-60 of copending U.S. Patent Application No. 13/961,835, 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 37-61 were rejected for statutory double patenting in view of claims 37-61 of co-pending U.S. Patent Application No. 13/961,818. 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

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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
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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

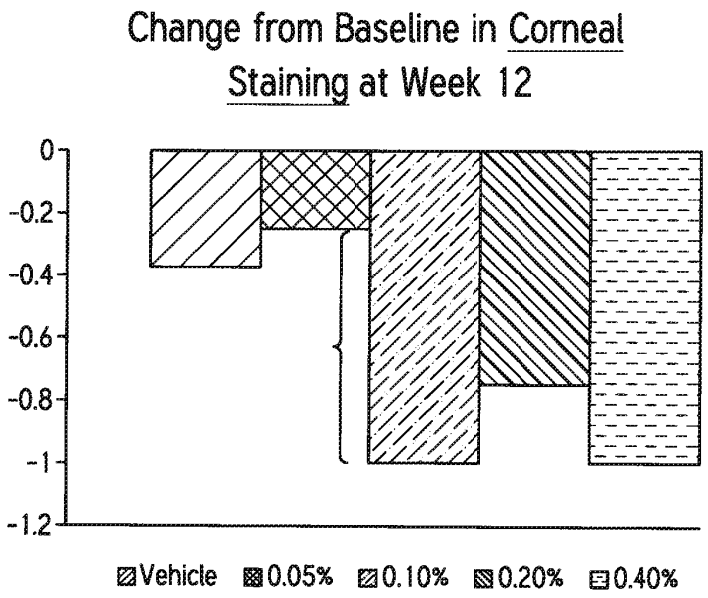


FIG. 1

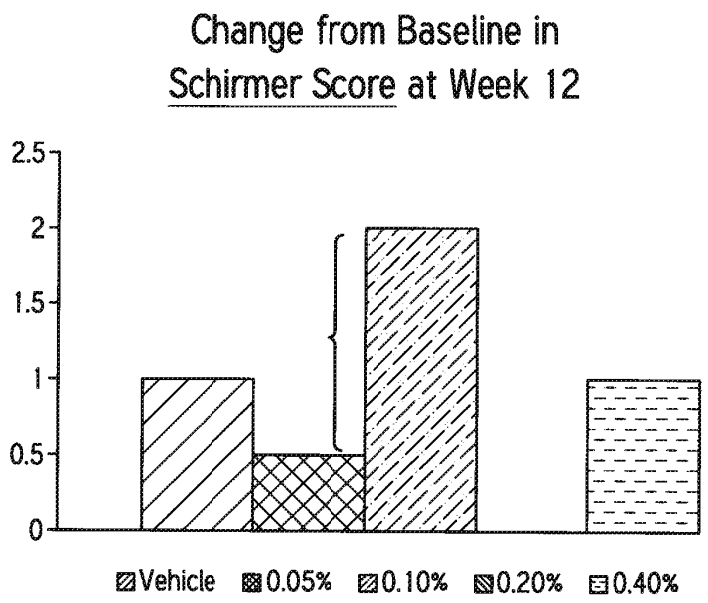


FIG. 2

EXHIBIT C

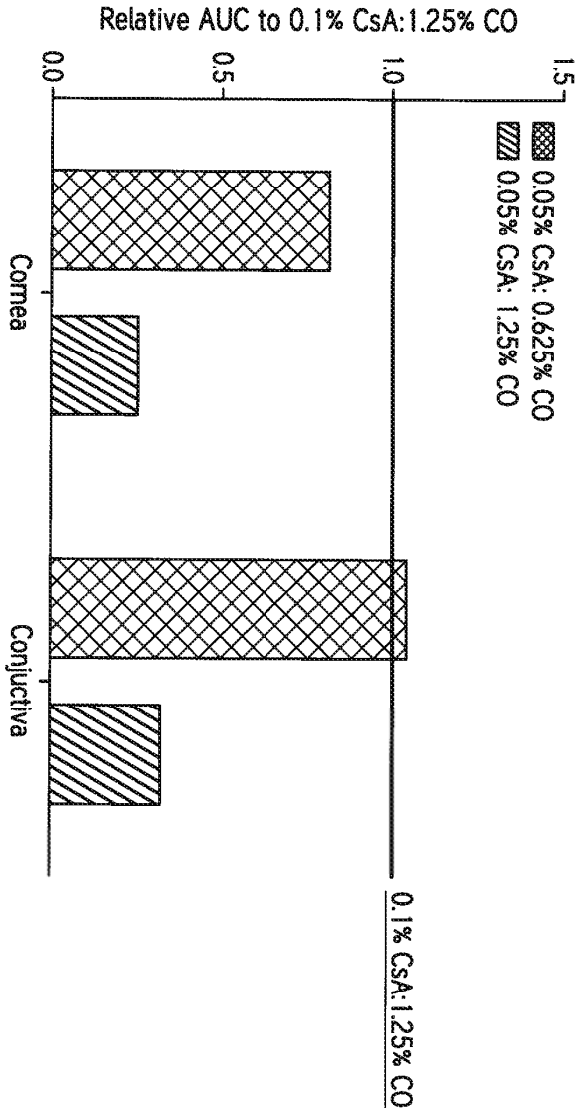

Relative AUC to 0.1% CsA:1.25% CO
0.0
0.5
1.0
1.5
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
Cornea
Conjuctiva
0.1% CsA:1.25% CO

EXHIBIT D

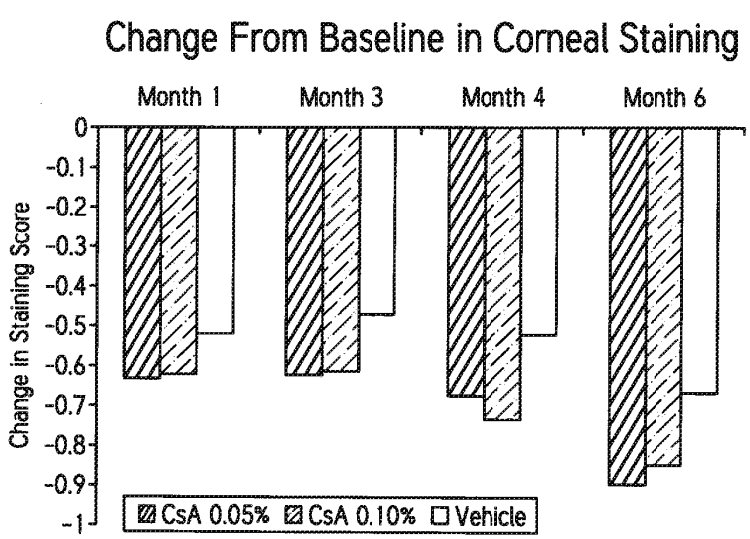

Change From Baseline in Corneal Staining
Month 1
Month 3
Month 4
Month 6
Change in Staining Score
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1
CsA 0.05%
CsA 0.10%
Vehicle

FIG. 1

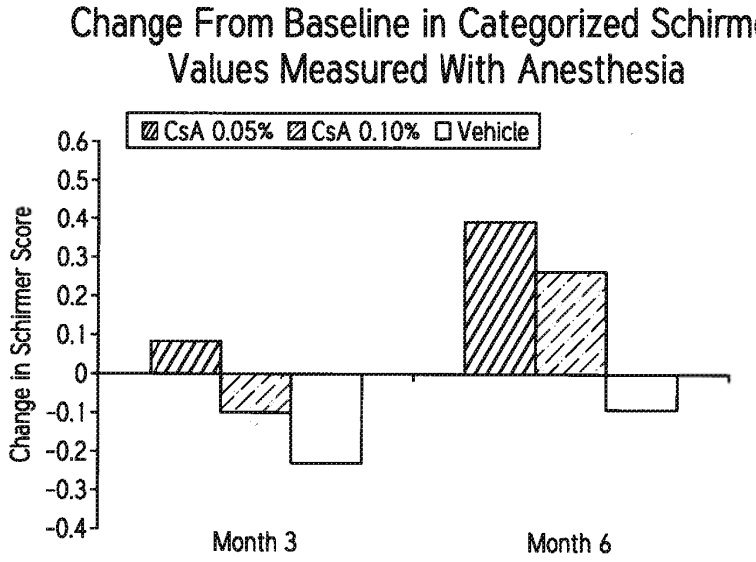

Change From Baseline in Categorized Schirmer Values Measured With Anesthesia
CsA 0.05%
CsA 0.10%
Vehicle
Change in Schirmer Score
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Month 3
Month 6

FIG. 2

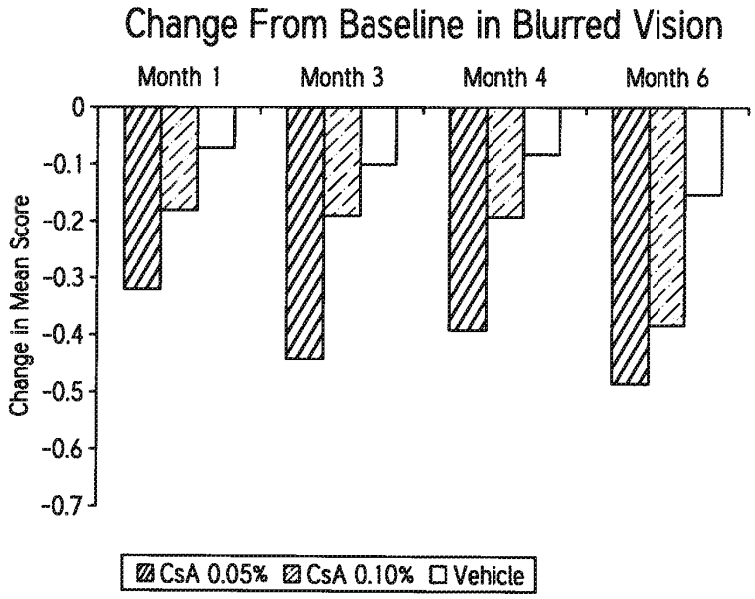

Change From Baseline in Blurred Vision
Month 1
Month 3
Month 4
Month 6
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
Change in Mean Score
CsA 0.05%
CsA 0.10%
Vehicle

FIG. 3

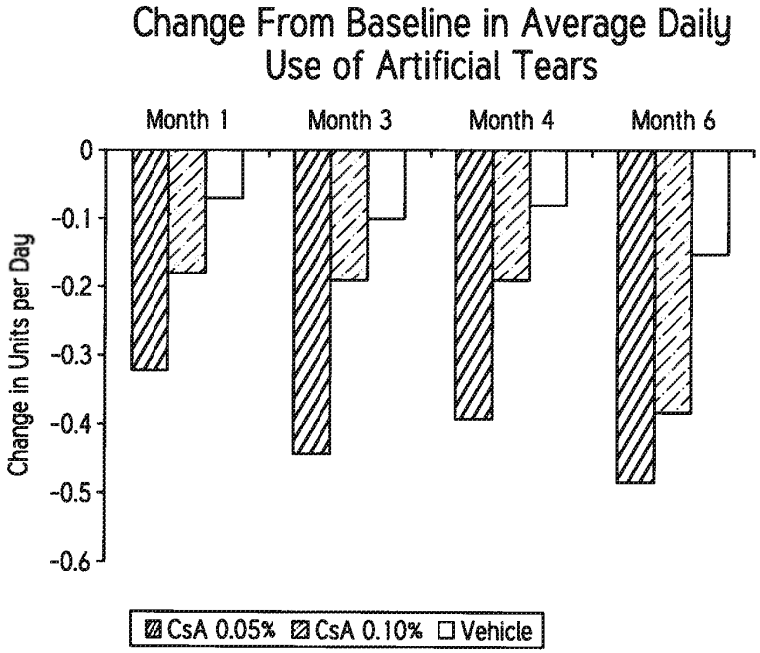

Change From Baseline in Average Daily Use of Artificial Tears
Month 1
Month 3
Month 4
Month 6
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
Change in Units per Day
CsA 0.05%
CsA 0.10%
Vehicle

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

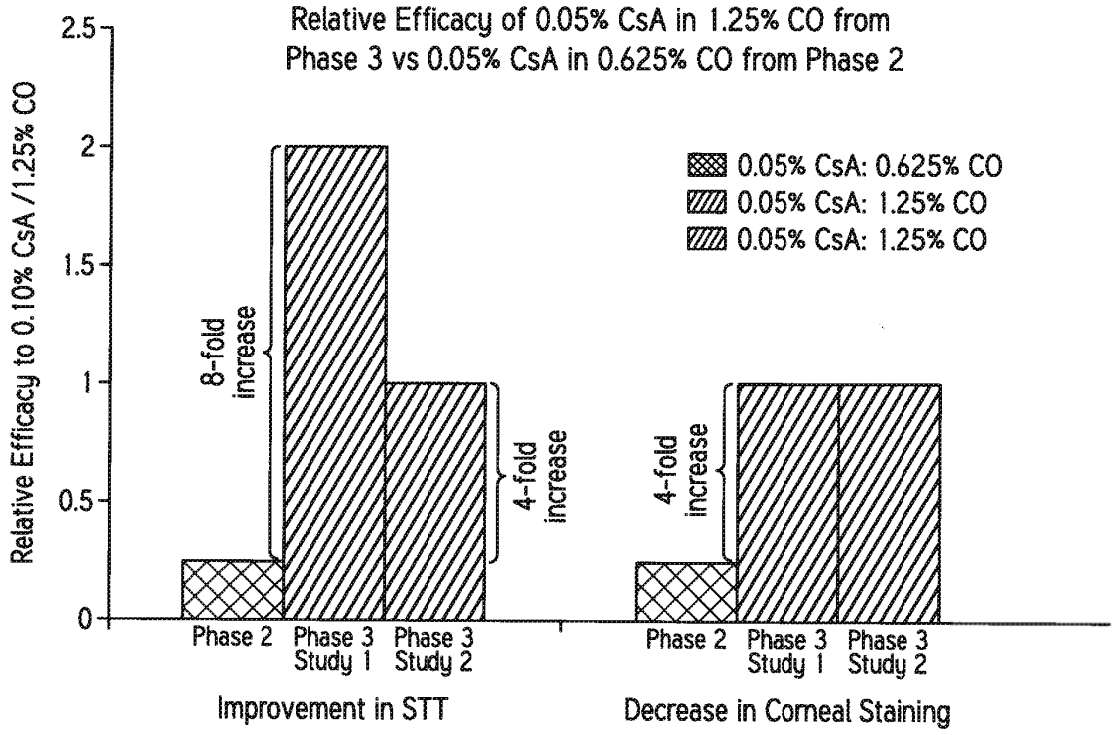

Relative Efficacy of 0.05% CsA in 1.25% CO from
Phase 3 vs 0.05% CsA in 0.625% CO from Phase 2
Relative Efficacy to 0.10% CsA /1.25% CO
2.5
2
1.5
1
0.5
0
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.05% CsA: 1.25% CO
8-fold increase
4-fold increase
4-fold increase
Phase 2
Phase 3 Study 1
Phase 3 Study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

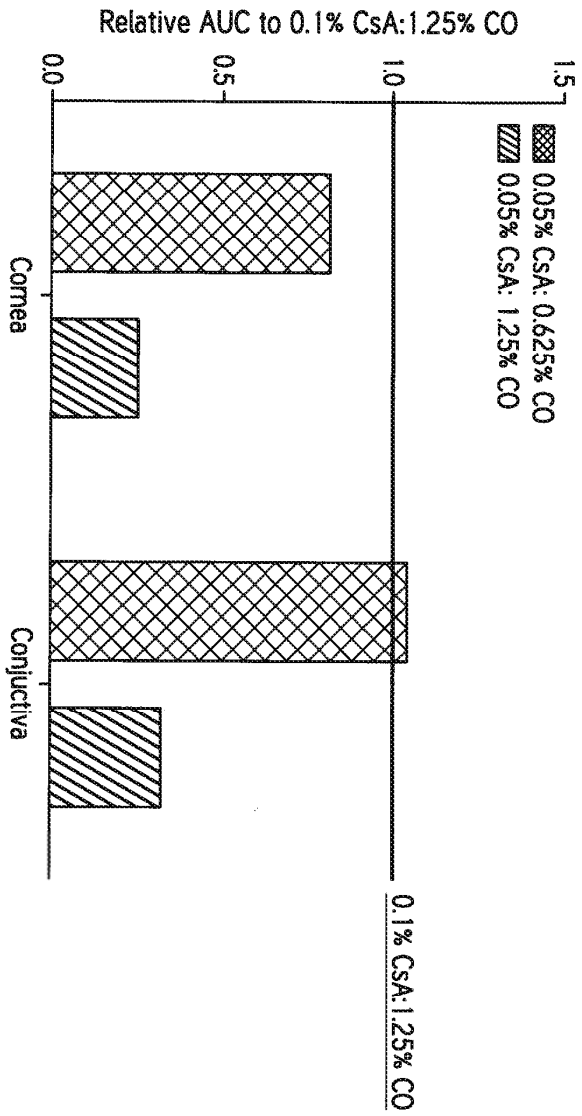

Relative AUC to 0.1% CsA:1.25% CO
0.0
0.5
1.0
1.5
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
Cornea
Conjuctiva
0.1% CsA:1.25% CO

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

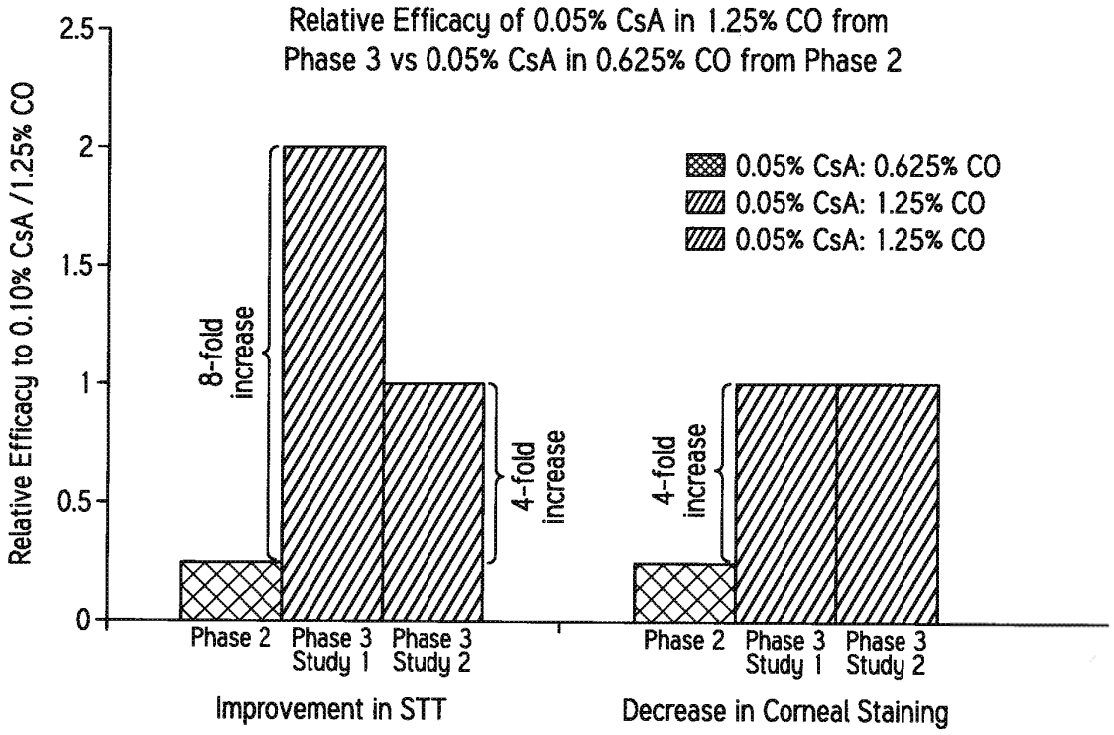

Relative Efficacy of 0.05% CsA in 1.25% CO from
Phase 3 vs 0.05% CsA in 0.625% CO from Phase 2
Relative Efficacy to 0.10% CsA /1.25% CO
2.5
2
1.5
1
0.5
0
0.05% CsA: 0.625% CO
0.05% CsA: 1.25% CO
0.05% CsA: 1.25% CO
8-fold increase
4-fold increase
4-fold increase
Phase 2
Phase 3 Study 1
Phase 3 Study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

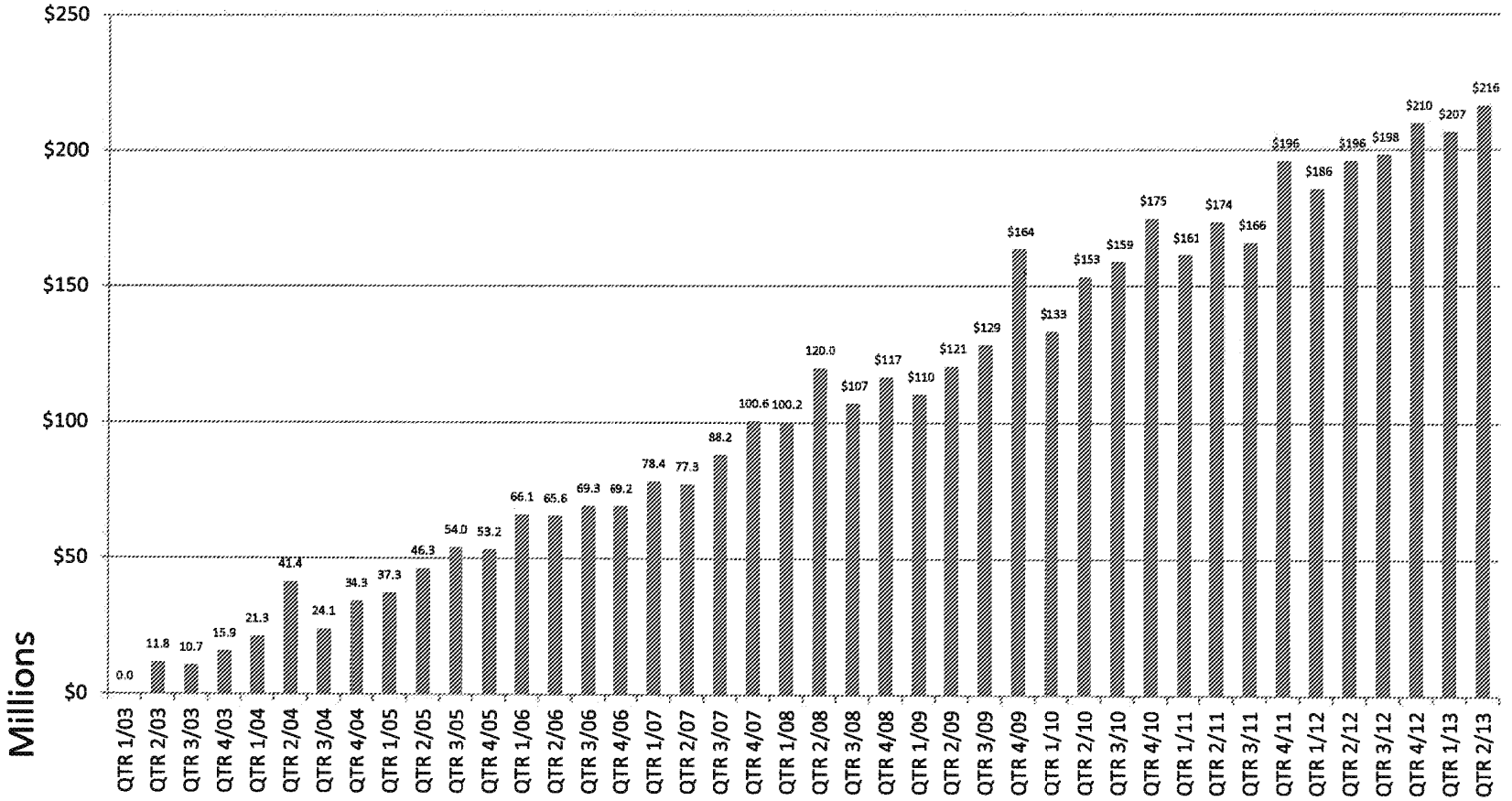
- Experience selling therapeutic products in various disease states including: Allergy, Asthma, Diabetes, Arthritis and Osteoporosis.
- Nova Award 2000: National award recognizing outstanding sales performance for a new associate.

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/daily21.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
Home Address:	1843 Temple Hills Laguna Beach, CA 92651
Office Telephone:	(401) 495-2395
Cell Telephone:	(313) 516-6924
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:

1. Ocular Therapy chapter in: Oréfice, Fernando: Uveíte: Clínica e Cirúrgica. Ed. Cultura Médica. Published June 2000.
2. New Concepts in the Pathogenesis, Diagnosis and Treatment of Dry Eye. Ocular Surgery News Monograph; Slack Incorporated. July 1, 1999

3. Schiffman RM: Glaucoma, Ophthalmology chapter in Noble, John: Textbook of Primary Care Medicine. 2nd Edition. 1996. Mosby-Year Book, Inc. 1471-9.

JOURNAL PUBLICATIONS:

1. Day D.G., Walters T.R., Schwartz G.F., Mundorf T.K., Liu C., Schiffman R.M., Bejanian M. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. Br J Ophthalmol. 2013 Jun 6. [Epub ahead of print]

2. Callanan DG, Gupta S, Boyer DS, Ciulla TA, Singer MA, Kuppermann BD, Liu CC, Li XY, Hollander DA, Schiffman RM, Whitcup SM; Ozurdex PLACID Study Group. Dexamethasone Intravitreal Implant in Combination with Laser Photocoagulation for the Treatment of Diffuse Diabetic Macular Edema. Ophthalmology. 2013 May 22. S0161-6420(13)00152-8.

3. Katz LJ, Rauchman SH, Cottingham AJ Jr, Simmons ST, Williams JM, Schiffman RM, Hollander DA. Fixed-combination brimonidine-timolol versus latanoprost in glaucoma and ocular hypertension: a 12-week, randomized, comparison study. Curr Med Res Opin. 2012 May;28(5):781-8

4. Katz, L.J., Rauchman, S.H., Cottingham Jr., A.J., Simmons, S.T., Williams, J.M., Schiffman, R.M., Hollander, D.A. Fixed-combination brimonidinetimolol versus latanoprost in glaucoma and ocular hypertension: A 12-week, randomized, comparison study. Current Medical Research and Opinion 28 (5) , pp. 781-788

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7. Xu, K., McDermott, M., Villanueva, L., Schiffman, R.M., Hollander, D.A. Ex vivo corneal epithelial wound healing following exposure to ophthalmic nonsteroidal anti-inflammatory drugs. Clin Ophthalmol 2011 5 (1), pp. 269-274.

8. Donnenfeld, E.D., Nichamin, L.D., Hardten, D.R., Raizman, M.B., Trattler, W., Rajpal, R.K., Alpern, L.M., Felix C, Bradford RR, Villanueva L, Hollander DA, Schiffman, R.M. Twice-daily, preservative-free ketorolac 0.45% for treatment of inflammation and pain after cataract surgery. Am J Ophthalmol 2011 151 (3):420-426.

9. Spaeth G, Bernstein P, Caprioli J, Schiffman RM. Control of Intraocular Pressure and Intraocular Pressure Fluctuation with Fixed Combination Brimonidine–Timolol versus Brimonidine or Timolol Monotherapy. Am J Ophthalmol. 2011 January;151:93–99.

10. Attar, M., Schiffman, R., Borbridge, L., Farnes, Q., Welty, D. Ocular pharmacokinetics of 0.45% ketorolac tromethamine. Clin Ophthalmol 2010 4(1), pp. 1403-1408

11. Craven, E.R., Liu, C.-C., Batoosingh, A., Schiffman, R.M., Whitcup, S.M. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. Clin Ophthalmol 2010 4 (1):1433-1440

12. Olson, R., Donnenfeld, E., Bucci Jr., F.A., Price Jr., F.W., Raizman, M., Solomon, K., Devgan, U., Trattler W, Dell S, Wallace RB, Callegan M, Brown H, McDonnell PJ, Conway T, Schiffman RM,

Hollander, D.A. Methicillin resistance of Staphylococcus species among health care and nonhealth care workers undergoing cataract surgery. Clin Ophthalmol. 2010 4(1):1505-1514

13. Katz L, Cohen J, Batoosingh A, Felix C, Shu V, Schiffman R. Twelve-Month, Randomized Controlled Trial of the Efficacy and Safety of Bimatoprost 0.01%, 0.0125%, and 0.03% in Patients with Glaucoma or Ocular Hypertension. Am J Ophthalmol. 2010 April;149:661–671.

14. Lewis R, Gross R, Sall K, Schiffman R, Liu C-C, Batoosingh A, (for the Ganfort® Investigators Group II). The Safety and Efficacy of Bimatoprost/Timolol Fixed Combination: A 1-year Double-masked, Randomized Parallel Comparison to Its Individual Components in Patients With Glaucoma or Ocular Hypertension. J Glaucoma. 2010 August;19(6):424-426.

15. Sherwood MB, Craven ER, Chou C, DuBiner HB, Batoosingh AL, Schiffman RM, Whitcup SM. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006 Sep;124(9):1230-8.

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20. Whitcup SM, Bradford R, Lue J, Schiffman RM, Abelson MB. Efficacy and tolerability of ophthalmic epinastine: a randomized, double-masked, parallel-group, active- and vehicle-controlled environmental trial in patients with seasonal allergic conjunctivitis. Clin Ther. 2004 Jan;26(1):29-34.

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22. McDonnell PJ, Taban M, Sarayba MA, Schiffman RM, et al.: Dynamic Morphology of Clear Corneal Incisions. Ophthalmology. 2003 Dec;110(12):2342-8.

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31. Javitt JC, Schiffman RM: Clinical Success and Quality of Life with Brimonidine 0.2% or Timolol 0.5% used BID in Glaucoma or Ocular Hypertension: A Randomized Clinical Trial. J Glaucoma. 2000 Jun;9(3):224-34.

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37. Ben-Menachem T. McCarthy BD. Fogel R. Schiffman RM. Patel RV. Zarowitz BJ. Nerenz DR. Bresalier RS. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. Critical Care Medicine. 24(2):338-45, 1996 Feb.

38. Ward RE; Purves T; Feldman M; Schiffman RM; Barry S; Christner M; Kipa G; McCarthy BD; Stiphout R: Design considerations of CareWindows, a Windows 3.0-based graphical front end to a Medical Information Management System using a pass- through-requester architecture. Proc Annu Symp Comput Appl Med Care 1991; 564-8

39. Stiphout RM; Schiffman RM; Christner MF; Ward R; Purves TM: Medical Information Management System (MIMS) CareWindows. Proc Annu Symp Comput Appl Med Care 1991; 929-31

40. Gubbins G, Schiffman RM, Alipati R, Batra S.: Cocaine-Induced Hepatonephrotoxicity. Henry Ford Hospital Medical Journal 1990; 38:55-56.

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.