PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Patent No.: 9,248,191	Group Art Unit: 1676
Issue Date: February 2, 2016	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

REQUEST FOR CERTIFICATE OF CORRECTION

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

It is requested that a Certificate of Correction be issued correcting printing errors appearing in the above-identified United States patent.

Pursuant to 1.20(a), the examiner is authorized to charge the Certificate of Correction fee of $100.00 or any additional fees or credit overpayment to Deposit Account No. 010885.

Issuance of the Certificate of Correction would neither expand nor contract the scope of the claims as properly allowed, and re-examination is not required.

Respectfully submitted,

Date February 16, 2016

By: /Laura L. Wine/
Laura L. Wine
Reg. No.: 68681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Patent No.: 9,248,191	Group Art Unit: 1676
Issue Date: February 2, 2016	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the attached:

X Request for Certificate of Correction.
X Certificate of Correction Form - PTO-1050

Please charge any additional fees or credit overpayment to Deposit Account No. 010885.

Respectfully submitted,

/Laura L. Wine/

Date: February 16, 2016

By Laura L. Wine
Reg. No.:68681

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the first page, in field (63), in column 1, in "Related U.S. Application Data", line 4, delete "and" and insert - - which is - -, therefor.

On the Page 2, in column 2, under "Other Publications", line 9, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 1, under "Other Publications", line 52, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 1, under "Other Publications", line 61, delete "Muscosal" and insert - - Mucosal - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 24, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 28, delete "Polyocyethylene" and insert - - Polyoxyethylene - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 29, delete "PhysicoChemical" and insert - - Physico-Chemical - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 39, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 13, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 35, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 48, after "U.S." insert - - Re-Examination - -.

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Page 4, in column 2, under "Other Publications", line 10, delete "Allegran," and insert - - Allergan, - -, therefor.

On the Page 4, in column 2, under "Other Publications", line 43, delete "Occular" and insert - - Ocular - -, therefor.

On the Page 5, in column 1, under "Other Publications", line 58, after "Systane" insert - - Products, Systane - -.

On the Page 5, in column 1, under "Other Publications", line 59, delete "http;//" and insert - - http:// - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 22, delete "Waston" and insert - - Watson - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 31, delete "No." and insert - - Nos. - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 33, delete "5050)(2)(13)" and insert - - 505(j)(2)(B) - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 48, delete "5050)(2)(13)" and insert - - 505(j)(2)(B) - -, therefor.

In column 1, line 8, delete "13/961.828" and insert - - 13/961,828 - -, therefor.

In column 1, line 36, delete "a" and insert - - A - -, therefor.

In column 1, line 37, delete "a" and insert - - A - -, therefor.

In column 1, line 39, delete "2002," and insert - - 2002 - -, therefor.

In column 1, line 53, delete "al." and insert - - al, - -, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 2, line 65, delete "kerapoconjunctivitis," and
insert - - keratoconjunctivitis, - -, therefor.

In column 3, line 12, delete "clyclcosporin" and insert - - cyclosporin - -, therefor.

In column 3, line 52, delete "were" and insert - - are - -, therefor.

In column 4, line 23, After "more" insert - - of - -.

In column 5, line 9, delete "kerapoconjunctivitis," and
insert - - keratoconjunctivitis, - -, therefor.

In column 5, line 66, After "with" delete "a".

In column 6, line 3, delete "acetronitrile-based" and insert - - acetonitrile-based - -, therefor.

In column 9, line 20, delete "each" and insert - - such - -, therefor.

In column 9, line 48, delete "extant" and insert - - extent - -, therefor.

In column 9, line 60, delete "benefiting" and insert - - benefitting - -, therefor.

In column 10, line 22, delete "informing" and insert - - in forming - -, therefor.

In column 10, line 35, delete "amphorteric" and insert - - amphoteric - -, therefor.

In column 11, line 7, delete "methylhydroxyethlystarches" and
insert - - methylhydroxyethylstarches - -, therefor.

In column 11, line 10, delete "glucoaminoglycans" and
insert - - glycosaminoglycans - -, therefor.

In column 11, line 28, delete "2-methacrylolyoxyethlysulfonic" and
insert - - 2-methacryloyloxyethylsulfonic - -, therefor.

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 11, line 29, delete "2-methacryloyloxethylsulfonates" and insert - - 2-methacryloyloxyethylsulfonates - -, therefor.

In column 11, line 30, delete "2-hydroxyproplysulfonic" and insert - - 2-hydroxypropylsulfonic - -, therefor.

In column 11, line 45, delete "crosslinked" and insert - - cross-linked - -, therefor.

In column 12, line 9, delete "polyvinyl," and insert - - polyvinyl - -, therefor.

In column 13, line 1, delete "Disoxide," and insert - - Dioxide, - -, therefor.

In column 13, line 34, delete "materiel" and insert - - material - -, therefor.

In column 14, line 32, delete "Premulen ®" and insert - - Pemulen® - -, therefor.

In column 15, line 24, in Claim 1, delete "005%" and insert - - 0.05% - -, therefor.

In column 15, line 61, in Claim 11, delete "claim 2," and insert - - claim 6, - -, therefor.

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of Correction	1811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	24926019
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	16-FEB-2016
Filing Date:	21-MAR-2014
Time Stamp:	16:41:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	3850
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	COCAllergan17618CON6CON1 AP9248191.pdf	164544 896d1a453cf219586794f8fade9fefd8b525c808	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30499 77d8f5cf7d4c6377f431b5aca5d39b369a6900f5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	195043		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	02/02/2016	9248191	17618CON6CON1 (AP)	9616

51957 7590 01/13/2016

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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 Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Allergan, Inc., Irvine, CA;
Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 12/18/2015

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

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 12/18/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

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	$960	$0	$0	$960	03/18/2016

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 12/18/2015
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)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

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	$960	$0	$0	$960	03/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1676	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 credits 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 forms 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: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 12/18/2015

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

EXAMINER	
CORDERO GARCIA, MARCELA M	

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 12/18/2015

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

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B 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.

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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

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

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

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

Date of Interview: *11 December 2015*.

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: *All, in general*.

Identification of prior art discussed: *US 9,101,574*.

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

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: Applicant's representative contacted Examiner to discuss the outstanding rejection and Applicant's response. During the interview Examiner indicated that, upon consideration of the response, Applicant's arguments mailed on 10/22/2015 are deemed persuasive and the only outstanding rejection (112 2nd 1st paragraph) has been withdrawn. Further, on 12/14/2015, Examiner contacted Applicant's representative to discuss US 9,101,574 with regards to a potential ODP rejection. Applicant's representative argued that the claims in the instant application were non-obvious over those claimed on US '574 because the specific ranges of cyclosporin and castor oil were not taught, and such ranges were associated to unexpected efficacy results (See, e.g., Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed on 1/28/14 for parent U.S. Patent Application No. 13/961,828, and 6/10/15 Non-Final Office Action for the instant application,paragraph 13). Applicant's arguments were deemed persuasive.Thus no ODP rejection over US '574 has been required and the instant application is deemed in condition for allowance. Applicant's representative filed their arguments in a supplemental response dated 12/14/2015 (see also attached electronic communication and copy of the filed arguments).

Notice of Allowability	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	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 *10/22/2015 and 12/14/2015*.
   ☐ 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 *37-63*. 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 10/22/2015
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1676

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

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The closest prior art is that of Ding et al. (US 5,474,979). The declaration under 37 CFR 1.132 by Rhett M. Schiffman filed on 12/5/2013 (EXHIBIT 1 comprising EXHIBITS A-F) in parent case Application 13/961,828, of which this case is a CON, is deemed sufficient to overcome a potential 103 rejection of the instant claims over Ding et al. (US 5,474,979, cited in the instant IDS dated 3/28/2014) 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 by Mayssa Attar, filed on 12/5/2013 (EXHIBIT 2, comprising EXHIBITS A-D) in parent case Application 13/961,828, of which this case is a CON, is deemed sufficient to overcome a potential rejection of the instant claims based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/12/2013) because: 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)).

The same described unexpected results above obviate a potential ODP rejection over US 9,101,574 (see attached interview summary).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

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 1676

MMCG 12/2015

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

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

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

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

Date of Interview: *11 December 2015*.

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: *All, in general*.

Identification of prior art discussed: *US 9,101,574*.

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

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: Applicant's representative contacted Examiner to discuss the outstanding rejection and Applicant's response. During the interview Examiner indicated that, upon consideration of the response, Applicant's arguments mailed on 10/22/2015 are deemed persuasive and the only outstanding rejection (112 2nd 1st paragraph) has been withdrawn. Further, on 12/14/2015, Examiner contacted Applicant's representative to discuss US 9,101,574 with regards to a potential ODP rejection. Applicant's representative argued that the claims in the instant application were non-obvious over those claimed on US '574 because the specific ranges of cyclosporin and castor oil were not taught, and such ranges were associated to unexpected efficacy results (See, e.g., Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed on 1/28/14 for parent U.S. Patent Application No. 13/961,828, and 6/10/15 Non-Final Office Action for the instant application,paragraph 13). Applicant's arguments were deemed persuasive.Thus no ODP rejection over US '574 has been required and the instant application is deemed in condition for allowance. Applicant's representative filed their arguments in a supplemental response dated 12/14/2015 (see also attached electronic communication and copy of the filed arguments).

Notice of References Cited	Application/Control No. 14/222,478	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,101,574 B2	08-2015	Chang; James N.	A61K9/0048	1/1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Cordero Garcia, Marcela M.

From: Wine_Laura <Wine_Laura@Allergan.com>
Sent: Monday, December 14, 2015 4:27 PM
To: Cordero Garcia, Marcela M.
Cc: Stein_Maria
Subject: US 14/222,478 Courtesy Copy of Supplemental Response and Interview Summary
Attachments: US14-222478_Supplemental_Response.pdf

Dear Examiner Cordero,

Attached please find a courtesy copy of a Supplemental Response and Interview Summary that was filed today for US 14/222,478 (AGN Ref: 17618CON6CON1). Please be advised that I have already filed a communication today under MPEP 502.3 authorizing email communications in this patent application.

Please do not hesitate to contact me if you have any questions.

Best regards,

Laura

Laura Wine
Patent Counsel
Allergan, Inc.
Wine_Laura@allergan.com

2525 Dupont Drive
T2-7
Irvine, CA 92612
Tel: 714-246-6996
Fax: 714-796-3043

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	617	cyclosporin same (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:42
L2	95	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:43
L3	25	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:43
L9	37	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:51
L10	2	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) same ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:52
L11	33	"7288520"	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:56
L12	2	"7288520".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:56

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	7	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:44
L5	58	"5,578,586"	USPAT	ADJ	ON	2015/12/14 11:46
L6	1	"5,578,586".pn.	USPAT	ADJ	ON	2015/12/14 11:46
L7	12	(cyclosporin or cyclosporine) near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:50

L8	12	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:51

12/14/2015 12:17:09 PM

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG
EAST search (attached)	6/4/2015	MMCG
also ran PALM Inventor search	6/4/2015	MMCG
EAST updated (attached)	12/14/2015	MMCG
also updated PALM Inventor search	12/14/2015	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG
EAST updated	attached	12/14/2015	MMCG

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1676

CPC							
Symbol						**Type**	**Version**
A61K		47	/	02		F	2013-01-01
A61K		9	/	0048		I	2013-01-01
A61K		38	/	13		I	2013-01-01
A61K		47	/	44		I	2013-01-01
A61K		9	/	107		I	2013-01-01
A61K		47	/	10		I	2013-01-01
A61K		47	/	22		I	2013-01-01
A61K		47	/	32		I	2013-01-01
			/				
			/				
			/				
			/				
			/				
			/				
			/				

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676 (Primary Examiner)	12/14/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1676

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	20.5	A	6	1	K	38 / 13 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676	12/14/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1676

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676 (Primary Examiner)	12/14/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5578586		1996-11-26	Glonek et al	
	2					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478	Receipt date: 10/22/2015
Filing Date	2014-03-21	
First Named Inventor	Andrew Acheampong	
Art Unit	1676	
Examiner Name	CORDERO GARCIA, MARCELA M	
Attorney Docket Number	17618-US-CN6CN1-AP	

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	T[5]
	1	ALBIETZ, JULIE, Dry Eye: An Update on Clinical Diagnosis, Management and Promising New Treatments, Clin & Exp. Optometry, 2001, 4-18, 84	☐
	2	Allergan Dry Eye Product Portfolio Fact Sheet (http://www.allergan.com/assets/pdf/dry_eye_product_portfolio_fact_sheet.pdf), 4 Pages, 2015	☐
	3	Allergan, Inc. 2001 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 54 Pages	☐
	4	Allergan, Inc. 2002 Annual Report (http://agn.client.shareholder.com/financials.cfm), 52 Pages, 2015	☐
	5	Allergan, Inc. 2003 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 52 Pages	☐
	6	Allergan, Inc. 2004 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 16 Pages	☐
	7	Allergan, Inc. 2006 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
	8	Allergan, Inc. 2005 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 35 Pages	☐
	9	Allergan, Inc. 2009 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
	10	Allergan, Inc. 2010 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 206 Pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

	11	Allergan, Inc. 2011 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 174 Pages ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	12	Allergan, Inc. 2012 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	13	Allergan, Inc. 2013 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	14	American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology, 2013, 44 Pages	☐
	15	AUTRY, JILL ET AL, Mix It Up: When to Call a Compounding Pharmacist, Review of Optometry, July 15, 2012, 30-37, 149	☐
	16	Bausch and Lomb "Dry Eye Products," downloaded from Bausch and Lomb Website http://www.bausch.com/our-products/dry-eye-products/dry-eye-products, last accessed April 14, 2015, 2 Pages	☐
	17	Certain Ophthalmic Combination Drugs Containing a Steroid and Anti-Infective(s) for Human Use; Drug Efficacy Study Implementation; Amendment, Federal Register, 1982, 21296-21301, 47	☐
	18	Certain Steroid Preparations for Ophthalmic and/or Otic Use, Federal Register, 1976, 34340-34342, 41	☐
	19	CHANANA, GURMUKH ET AL, Particle Size Reduction of Emulsions By Formulation Design-II: Effect of Oil and Surfactant Concentration, PDA Journal of Pharmaceutical Science and Technology, 1995, 71-76, 49(2)	☐
	20	CHIDAMBARAM, N. ET AL, Effect of Nonionic Surfactant on Transport of Surface-Active and Non-Surface-Active Model Drugs and Emulsion Stability in Triphasic Systems, AAPS Pharmasci, 2000, 1-11, 2(3)	☐
	21	CHUNG, HESSON ET AL, Oil Components Modulate Physical Characteristics and Function of the Natural Oil Emulsions As Drug or Gene Delivery System, Journal of Controlled Release, 2001, 339-350, 71	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478	Receipt date: 10/22/2015
Filing Date	2014-03-21	
First Named Inventor	Andrew Acheampong	
Art Unit	1676	
Examiner Name	CORDERO GARCIA, MARCELA M	
Attorney Docket Number	17618-US-CN6CN1-AP	

	22	COLES, WILLIAM ET AL, Dynamics of Ocular Surface pH, British Journal of Ophthalmology, 1984, 549-552, 68 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	23	CTFA Becomes the Personal Care Products Council, 1 Page, 2015 (http://www.personalcarecouncil.org/ctfa-becomes-personal-care-products-council)	☐
	24	Curriculum Vitae of Christopher N. Ta, Ph.D., 23 Pages, 2015	☐
	25	Curriculum Vitae of Erning Xia, Ph.D., 17 Pages, 2015	☐
	26	Curriculum Vitae of Harry C. Boghigian, 11 Pages, 2015	☐
	27	DE PAIVA, C.S. ET AL, Rationale for Anti-Inflammatory Therapy in Dry Eye Syndrome, Arq. Bras. Oftalmol., 2008, 89-95, 71	☐
	28	Declaration of Christopher N. Ta, Ph.D., 57 Pages, 2015	☐
	29	Declaration of Erning Xia, Ph.D., 197 Pages, 2015	☐
	30	Declaration of Harry C. Boghigian, 37 Pages, 2015	☐
	31	Drugs@FDA: FDA Approved Drug Products, LACRISERT, downloaded from the FDA website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails, last accessed April 16, 2015, 2 Pages	☐
	32	Drugs@FDA: FDA Approved Drug Products, RESTASIS, downloaded from the FDA website http://www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm, last accessed April 14, 2015, 2 Pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

	33	Dry Eye Drop Symptom Relief Product information at Systane.com, Systane Products, Systane Ultra Lubricant Eye Drops, downloaded from Alcon website http://www.systane.com/Dry-Eye-Drop.aspx, last visited April 21, 2015, 2 Pages ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	34	FREEMAN, JERRE MINOR, The Punctum Plug: Evaluation of a New Treatment For The Dry Eye, Transactions American Academy of Ophthalmology and Otolaryngology, 1975, 874-879, 79	☐
	35	GILBARD, JEFFERY, Dry Eye, Blepharitis and Chronic Eye Irritation: Divide and Conquer, J Ophthalmic Nurs. Technol., 1999, 109-115, 18	☐
	36	GOTO, EIKI ET AL, Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction, Ophthalmology, 2002, 2030-2035, 109	☐
	37	INATOMI, TSUTOMU ET AL, Expression of Secretory Mucin Genes By Human Conjunctival Epithelia, Invest Ophthalmol Vis Sci, 1996, 1684-1692, 37	☐
	38	KUNERT, KATHLEEN ET AL, Analysis of Topical Cyclosporine Treatment of Patients With Dry Eye Syndrome, Arch Ophthalmol, 2000, 1489-1496, 118	☐
	39	Lacrisert (hydroxypropyl cellulose ophthalmic insert) Approved Label, downloaded from the FDA website http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/018771s0171bl.pdf, last accessed April 14, 2015, 7 Pages	☐
	40	Learn more about Systane Gel Drops at Systane.com, Systane Products, Systane Gel Drops, Downloaded From Alcon Website http://www.systane.com/Gel-Drops.aspx, last accessed April 21, 2015	☐
	41	LEMP, MICHAEL, Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, CLAO, 1995, 221-232, 21	☐
	42	LIU, KEVIN ET AL, Synthetic Approaches to the 2010 New Drugs, Bioorganic & Medicinal Chemistry, 2012, 1155-1174, 20	☐
	43	MAISSA, CECILE ET AL, Effect of Castor Oil Emulsion Eyedrops on Tear Film Composition and Stability, Contact Lens &Anterior Eye, 2010, 76-82, 33	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

	44	MANN, ELAINE, Drugs Used in the Treatment of Dry Eye Syndrome, Anti-Inflammatory Drugs and Topical Anti-Allergy Drugs, Continuing Education & Training, 2007, 30-40 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	45	MURPHY, ROB ET AL, The Once and Future Treatment of Dry Eye, Review of Optometry January 2000 Cover Focus, 2000, 6 Pages (http://legacy.revoptom.com/archive/FEATURES/ro0200f6.htm)	☐
	46	NAPPER, G. ET AL, Ocular Therapeutics, Clin & Exp Optometry, 2003, 414-415, 86	☐
	47	Ophthalmic Drug Products for Over-The-Counter Human Use; Final Monograph, Federal Register, 1988, 7076-7093 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-theCounterOTCDrugs/StatusofOTCRulemakings/ucm071941.htm), 53	☐
	48	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, patent and exclusivity data for Restasis, downloaded from FDA website http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050790&Product_No=001&table1=OB_Rx, last accessed January 12, 2015	☐
	49	Personal Care Production Council (http://personalcarecouncil.org/) 3 Pages, 2015	☐
	50	PFLUGFELDER, STEPHEN ET AL, The Diagnosis and Management of Dry Eye: A Twenty-Five-Year Review, Cornea, 2000, 644-649, 19(5)	☐
	51	Restasis Approved Label, download from the Allergan Website (https://www.restasisprofessional.com/RestasisProfessional/FullPrescribingInformation) 6 Pages, 2015	☐
	52	ROWE, E.L., Effect of Emulsifier Concentration and Type on the Particle Size Distribution of Emulsions, Journal of Pharmaceutical Science, 1965, 260-264, 54	☐
	53	SOLOMON, ABRAHAM ET AL, Doxycycline Inhibition of Interleukin-1 in the Corneal Epithelium, Ophthalmol Vis Sci, 2000, 25544-2557, 41	☐
	54	Systane Lubricant Eye Drops Information at Systane.com, Systane Products, Systane Balance Lubricant Eye Drops, Download from Alcon Website http://www.systane.com/systane-Balance-Lubricant-Eye-Drops.aspx, last accessed April 21, 2015	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478	Receipt date: 10/22/2015
Filing Date	2014-03-21	
First Named Inventor	Andrew Acheampong	
Art Unit	1676	
Examiner Name	CORDERO GARCIA, MARCELA M	
Attorney Docket Number	17618-US-CN6CN1-AP	

	55	Systane Lubricant Eye Gel, Systane Products, Systane Lubricant Eye Gel, Downloaded from Alcon Website http:// www.systane.com/systane-Lubricant-Eye-Gel.aspx, last visited April 21, 2015, 2 pages ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	56	TABAN, MEHRYAR ET AL, Update on Punctal Plugs, Comp. Ophthalmology Update, 2006, 205-2012, 7(5)	☐
	57	TURNER, KATHLEEN ET AL, Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion, Cornea, July 2000, 492-496, 19(4)	☐
	58	YEH, STEVEN ET AL, Apoptosis of Ocular Surface Cells in Experimentally Induced Dry Eye, Invest Ophthalmol Vis, 2003, 124-129, 44	☐
	59	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, pages 1 - 43, Dated September 18, 2015	☐
	60	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, pages 1 - 46, Dated September 17, 2015	☐
	61	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, pages 1 - 46, Dated September 17, 2015	☐
	62	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, pages 1 - 43, Dated September 22, 2015	☐
	63	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, pages 1 - 47, Dated September 18, 2015	☐
	64	In the United States District Court for the Eastern District of Texas Marshall Division, Allergan, Inc. (Plaintiff) v. Actavis, Inc., Watson Laboratories, Inc., and Actavis Pharma, Inc. (f/k/a Watson Pharma, Inc.) (defendants), C.A. No. 2:14-cv-638-JRG-Lead Case Consolidated with 2:14-cv-188-JRG, Actavis, Inc., Waston Laboratories, Inc., and Actavis Pharma, Inc.'s Invalidity Contentions Pursuant to Local Patent Rules 3-3 and 3-8, pages 1-74, dated October 15, 2014	☐
	65	Letter from Victor Ramsaywak of Apotex, Inc., Notice of Certification Under 21 USC Section 355(j)(2)(B)(ii) (Section 505(j)(2)(B(ii) of the Federal Food, Drug and Cosmetic Act(and 21 CFR Section 314.95 dated July 23, 2015, pages 1-116	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

	66	Letter from Shashank Upadhye, Counsel for InnoPharma, Inc., of Amin Talati & Upadhye, Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Patent Nos. 5,474,979; 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, dated July 31, 2015, pages 1-68 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	67	Letter from J.C. Rozendaal of Kellogg, Huber, Hansen, Todd, Evans & Figel, PLLC, Notice of ANDA No. 203880 Concerning Cyclosporine Ophthalmic Emulsion, 0.05% with Paragraph IV Certification Concerning U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 dated July 22, 2015, pages 1-40	☐
	68	Letter from Joseph M. Reisman, Counsel for Mylan Pharmaceuticals Inc., of Knobbe Martens, Cyclosporine Emulsion 0.05%, Route of Administration: Ophthalmic, U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930, Notice of Paragraph IV Certification, dated July 20, 2015, pages 1-226	☐
	69	Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act - 21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated July 10, 2015, pages 1-26	☐
	70	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, Pages 1-63, Dated June 4, 2015	☐
	71	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, Pages 1-63, Dated June 4, 2015	☐
	72	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, Pages 1-63, Dated June 4, 2015	☐
	73	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, Pages 1-63, Dated June 4, 2015	☐
	74	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, Pages 1-63, Dated June 4, 2015	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature	/Marcela Cordero Garcia/	Date Considered	12/11/2015

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478	Receipt date: 10/22/2015
Filing Date	2014-03-21	
First Named Inventor	Andrew Acheampong	
Art Unit	1676	
Examiner Name	CORDERO GARCIA, MARCELA M	
Attorney Docket Number	17618-US-CN6CN1-AP	

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

CERTIFICATION STATEMENT

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

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-10-22
Name/Print	Laura L. Wine	Registration Number	68,681

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

Receipt date: 10/22/2015

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.

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

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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.

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 12/18/2015
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.

Laura L. Wine	(Depositor's name)
Laura L. Wine	(Signature)
December 18, 2015	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

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	$960	$0	$0	$960	03/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1676	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 Laura L. Wine
2 Joel B. German
3 Debra D. Condino

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: Allergan, Inc.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Irvine, CA

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 credits any overpayment, to Deposit Account Number 010885 (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 forms 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: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Laura L. Wine/ Date December 18, 2015
Typed or printed name Laura L. Wine Registration No. 68681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

COMMENTS ON EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE AND INTERVIEW SUMMARY

Mail Stop - Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Statement of Reasons for Allowance in the Notice of Allowance mailed December 18, 2015, Applicant respectfully submits the following comments.

A Summary of Interviews begins on page 2 of this paper.

Comments on Statement of Reasons for Allowance begin on page 3 of this paper.

SUMMARY OF TELEPHONE INTERVIEWS

Attendees, Date and Type of Interviews

Telephone interviews were conducted on December 10 and 11 and attended by Examiner Marcela M Cordero Garcia and Laura L. Wine.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37, 49, 53, and 57.

Principal Arguments and Other Matters

Laura L. Wine and Examiner Cordero Garcia discussed the rejection under 35 U.S.C. § 112, first paragraph in the June 10, 2015 Non-Final Office Action. The Applicants argued that the Claims of the present application contained proper written description support.

Results of Interviews

It was agreed that the Applicants' arguments were persuasive to overcome the rejections of record in the June 10, 2015 Non-Final Office Action.

COMMENTS ON STATEMENTS OF REASONS FOR ALLOWANCE

Applicants respectfully submit the following comments on the Examiner's Statement of Reasons for Allowance.

To the extent that there is any implication in such Statement that the patentability of the claims rests on the recitation of a single feature or the combination of particular features, Applicants respectfully disagree, since patentability rests on each claim taken as a whole. For example, Applicants submit that there are additional features from the claims that are not set forth in the cited art. Further, the Examiner's Statement refers to certain features of the claims. To the extent that the Examiner's Statement omits claim elements, groups claims together, or identifies purportedly distinguishing features of a claim or a group of claims, Applicants respectfully disagree with the Examiner's Statement. Rather, Applicants submit that the claims are allowable, because each claim, taken as a whole, recites a unique combination of features that is not anticipated or rendered obvious by the prior art.

Applicants also hereby traverse and respectfully reserve the right to traverse the characterizations of what any particular reference shows or teaches, or what any combination of references shows or teaches, or the appropriateness of combining references, and reserve the right to continue to do so in the future. In addition, Applicants respectfully traverse any characterizations of which references are deemed to be the closest prior art. Further, by making certain amendments to the claims, Applicants are not conceding that previously pending claims are not patentable. Rather, the amendments are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the application's disclosure. Moreover, any arguments in support of patentability and based on a portion of a claim should not be taken as founding patentability solely on the portion in question; rather, it is

the combination of features or acts recited in a claim taken as a whole which distinguishes it over the identified references.

Applicants attach herewith payment of the issue fee and requests that the application proceed to issuance. Should the Examiner have any concerns, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

/Laura L. Wine/

Date: December 18, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	24411956
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	18-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	14:58:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	1432
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	17618CON6CON1_PTOL85.pdf	114712 1a8ae8c8cdf1dc4c1ec78dee094011ca6a5366fa	no	1
Warnings:					
Information:					
2	Applicant summary of interview with examiner	17618CON6CON1_INTERVIEW_SUMMARY_AND_RESPONSE_TO_ALLOWANCE.pdf	109453 0176adcfd771cd341daca744d7129c5923dad44f	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30866 3029a192d6d44c93ed8962d17662e0725157001a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	255031		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

COMMUNICATION UNDER MPEP 502.3

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

Dear Sir:

Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file.

Respectfully submitted,

/Laura L. Wine/

Date: December 14, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	24351915
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Lauren Barberena
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	14-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	15:06:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	17618CON6CON1_COMM_UNDER_MPEP_5023.pdf	95433 e8815c4fd1e2825c2780349940b2a4fd8401aa3a	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	95433

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

SUPPLEMENTAL AMENDMENT

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

Dear Sir:

These papers are filed as a supplement to the 10/22/15 Response to the Non-Final Office Action filed mailed June 10, 2015.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

A telephonic interview was conducted on December 14, 2015 and was attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed.

References Discussed

U.S. Patent No. 9,101,574 ("the '574 patent").

Principal Arguments and Other Matters

Claim 1 of the '574 patent was discussed as grounds for a potential obviousness-type double patenting rejection. The Applicants disagreed that a double patenting rejection was proper, because the pending Claims of the present application are patentably distinct over Claim 1 of the '574 patent.

Results of Interview

It was agreed that the Applicants' representative would file a supplemental amendment, presenting arguments discussed during the interview.

REMARKS

This Reply is a supplement to the 10/22/15 Response to the Non-Final Office Action filed sent 6/10/15 The Applicants respectfully submit that the claims are in condition for allowance.

Obviousness-Type Double Patenting

The Examiner has brought Claim 1 of U.S. Patent No. 9,101,574 ("the '574 patent") to the Applicants' attention as a potential grounds for rejection of the pending Claims for obviousness-type double patenting. The Applicants disagree with the proposed grounds of rejection.

The Applicants submit that an obviousness-type double patenting rejection over Claim 1 of the '574 patent would be improper. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by or would have been obvious over, the reference claims. MPEP § 804. The Applicants submit that the pending Claims of the current application are patentably distinct from Claim 1 of the '574, because the Claims of the present application recite several non-obvious elements not recited in Claim 1 of the '574 patent.

As a non-limiting example, each pending independent claim (i.e., Claims 37, 49, 53, and 57) recites therapeutic methods including topical administration of a topical ophthalmic emulsion, where the emulsion comprises cyclosporin A in an amount of about 0.05% by weight and castor oil in an amount of about 1.25% by weight. The non-obviousness of this selection of the specific percentages of cyclosporin A and castor oil within the topical ophthalmic emulsion has been established throughout the prosecution of related cases (*See*, *e.g.*, Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed on 1/28/14 for parent U.S. Patent Application No. 13/961,828), and has been

acknowledged by the Examiner in the present case (see 6/10/15 Non-Final Office Action, paragraph 13).

Claim 1 of the '574 patent does not recite these specific amounts of cyclosporin A and castor oil, and instead recites: "An ophthalmically acceptable emulsion comprising from about 0.001% to 0.4% cyclosporin A, castor oil, Polysorbate 80, Pemulen, and a cellulose derivative selected from the group consisting of hydroxypropylmethyl cellulose and carboxymethyl cellulose." Nothing in this claim would lead one of skill in the art to modify Claim 1 of the '574 patent to arrive at the currently claimed methods, and the non-obviousness of the selection of the specific amounts of cyclosporin A and castor oil has already been established. Thus, because the pending Claims in the present application are patentably distinct from Claim 1 of the '574 patent, an obviousness-type double patenting rejection would be improper and thus should not be made.

There are several other patentably distinct features of the currently pending Claims, and the Applicants reserve the right to argue these additional features at a later date, if necessary.

CONCLUSION

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: December 14, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	24354408
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	14-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	16:23:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618C6C1_Supplemental_Response.pdf	116116 e625aef0b10f5d9cf1a9041cc8491beccc539191	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	5
Warnings:			
Information:			
	Total Files Size (in bytes):	116116	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	23869531
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	21:50:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	65-Apotex_Para_IV.pdf	10222550 2216ec48d12acdfb882ce087ce35fe95d6b72c64	no	116

Warnings:	
Information:	

2	Non Patent Literature	66-2015-08-03_ParaIV_Ltr_Inno Pharma.pdf	7755028 821cd9b7d467d1764ca4351d3d843b6963c677b8	no	98
Warnings:					
Information:					
3	Non Patent Literature	67-2015-07-23_ParaIV_Ltr_Teva_RESTASIS.pdf	3331902 37c7fce52b8af9dfcb6aad200fda2d86c4e4938f	no	40
Warnings:					
Information:					
4	Non Patent Literature	68-2015-07-21_ParaIV_Ltr_Mylan_RESTASIS.pdf	11764636 bc9b70c403c142b0f108edd182db6e4c892b5f54	no	226
Warnings:					
Information:					
5	Non Patent Literature	69-Akorn-Para-IV.pdf	6728857 11f0e1ae4d4cf5098dda70fac11fa81ff8238111	no	26
Warnings:					
Information:					
6	Non Patent Literature	70-IPR2015-01278-Petition-for-Inter-Partes-Review.pdf	8731940 47bd495e5e19eff8d2eddab11a213f5c8fd90ad9	no	63
Warnings:					
Information:					
7	Non Patent Literature	71-IPR2015-01282-Petition-for-Inter-Partes-Review.pdf	258252 5615296987403526e24a08f2003371a55aa24703	no	63
Warnings:					
Information:					
8	Non Patent Literature	72-IPR2015-01283-Petition-for-Inter-Partes-Review.pdf	235680 2275320de355a4343841b6945dc781cc1c62d174	no	63
Warnings:					
Information:					
9	Non Patent Literature	73-IPR2015-0128-Petition-for-Inter-Partes-Review.pdf	175795 866e8f81e46a3243c0e05cf645c69a275017f4a0	no	63
Warnings:					
Information:					
10	Non Patent Literature	74-IPR2015-01286-Petition-for-Inter-Partes-Review.pdf	238844 754da1057b602129c05bb6346f6e1060b387ce18	no	63
Warnings:					
Information:					

11	Non Patent Literature	8-2005AnnualReport.pdf	3116041 069deaba3a472848bf122ee4b8c6d8fe0b0684cb	no	35
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
12	Non Patent Literature	9-2009AnnualReport.pdf	2212691 28549e26209dcbd5e2f23d51a78e077b35d1d8a2	no	18
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
13	Non Patent Literature	25-Xia2015.pdf	1315020 caaf25594ac474c9d5a3bc1f98e894ad1ef234ff6	no	17
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
14	Non Patent Literature	12-2012AnnualReport.pdf	2295053 73c75e077fc203e2891364bd6ca51169e8064b6c	no	28
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
15	Non Patent Literature	7-2006AnnualReport.pdf	1569143 b5fe6833c3dc1870228f905e4f2fa8ac9afccbc4	no	18
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
			Total Files Size (in bytes):	59951432	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO OFFICE ACTION DATED JUNE 10, 2015

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

Dear Sir:

These papers are filed in reply to the Office Action mailed June 10, 2015.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

A Summary of Interview begins on page 2 of this paper.

Remarks begin on page 3 of this paper.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

A Telephonic interview was conducted on August 14, 2015 and was attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed.

Principal Arguments and Other Matters

The rejection under 35 U.S.C. § 112, first paragraph was discussed. The Applicants' representative argued that proper written description support for the Claims was present in the specification as originally filed. The Applicants pointed to further examples of support for the Claims in the specification, including, but not limited to, page 3, line 29 – page 4, line 19.

Results of Interview

It was agreed that the Applicants' representative would file a response to the Office Action, presenting arguments discussed during the interview.

REMARKS

This Reply responds to the Office Action sent June 10, 2015, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement. As will be explained in further detail below, the Applicants submit that the Claims are properly supported by the specification as originally filed, and that it is clear that the inventors had possession of the invention claimed at the time of filing of the application.

The Claims Comply with the Written Description Requirement

Written Description Requirement

According to the MPEP, an objective standard for determining compliance with the written description requirement, which is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co.v.Far-Mar-Co., Inc.,* 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). *MPEP§ 2163.02.*

The Applicants submit that the specification as filed reasonably conveys that the inventors were in possession of the claimed subject matter, and that the description clearly allows persons of ordinary skill in the art to recognize that they invented what is claimed. The specification adequately describes the claimed invention.

Looking at the specification, it is clear that the inventors had invented a method of treating dry eye disease using formulations disclosed, as well as methods incorporating administration of the cyclosporin formulations at a frequency of twice a day:

> The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation**. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.**

Page 9, line 25 – page 10, line 7 of the specification of the present application as originally filed (emphasis added).

Another benefit recognized by the inventors was the efficacy of the methods of administering the cyclosporin formulations compared to formulations compared to formulations containing 0.1% cyclosporin:

> In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.
>
> It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. **For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the**

presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition.

Page 3, line 29 – page 4, line 19 of the specification of the present application as originally filed (emphasis added).

This benefit, as well as other benefits compared to a formulation comprising about 0.1 % cyclosporin by weight and about 1.25% castor oil by weight are further described later in the specification under Example 1, which compared the efficacy of Composition I and Composition II, two formulations administered to human patients in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I	Composition II
	wt%	wt%
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Purmulen®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, **provides overall efficacy in treating dry eye disease substantially equal** to that of Composition I.

Page 26, lines 22-27 of the specification of the present application as originally filed (emphasis added).

> In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, **provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye,** for example, as measured by slit-lamp techniques to monitor the composition in the eye for phase separation.

Page 27, lines 10 – 17 of the specification of the present application as originally filed (emphasis added).

The Applicants submit that, based on at least the disclosures above, one of skill would reasonably conclude and recognize that the inventors of the patent had possession of what is claimed in the pending Claims. The specification demonstrates that the inventors possessed their invention – the Claims recite a method of treating dry eye disease by administering a formulation at the frequency of twice a day, wherein the method provides overall efficacy substantially equal to administration of a second formulation comprising cyclosporin in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight at a frequency of twice a day – and the specification discloses such a method.

The Standards for Compliance with the Written Description Requirement Stated in the Office Action are Improper

The Office Action states that the Claims lack written description support because the claims lack ipsis verbis support in the specification as originally filed. See 6.10.2015 Non-Final Office Action at paragraph 8. However, the Applicants submit that the Office Action's proposed requirement for explicit, ipsis verbis, support is <u>not</u> the standard under the law, the CFR, or the MPEP. Several Federal Circuit decisions have confirmed that "ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead the disclosure need only reasonably convey to persons skilled in the

art that the inventor had possession of the subject matter in question." *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996).[1]

As described above, it is clear from reviewing the specification that the Applicants were in possession of the subject matter claimed, and thus satisfy the written description requirement.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement be withdrawn.

CONCLUSION

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 22, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

[1] *See also In re* Alton, 76 F3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) ("If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.").

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
			Total in USD ($)	**600**

Electronic Acknowledgement Receipt

EFS ID:	23869604
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine
Filer Authorized By:	
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	22:07:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$600
RAM confirmation Number	6696
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON6CON1_Response_to_NFOA_dated_06_10_15.pdf	550991 c15c8e295df453eee9886a7504f201029207fb42	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant summary of interview with examiner	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	7

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30860 e80ac67b6dcade84fc7fd5677bbd3c423e87ab81	no	2

Warnings:

Information:

Total Files Size (in bytes):	581851

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5578586		1996-11-26	Glonek et al	
	2					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ALBIETZ, JULIE, Dry Eye: An Update on Clinical Diagnosis, Management and Promising New Treatments, Clin & Exp. Optometry, 2001, 4-18, 84	☐
	2	Allergan Dry Eye Product Portfolio Fact Sheet (http://www.allergan.com/assets/pdf/dry_eye_product_portfolio_fact_sheet.pdf), 4 Pages, 2015	☐
	3	Allergan, Inc. 2001 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 54 Pages	☐
	4	Allergan, Inc. 2002 Annual Report (http://agn.client.shareholder.com/financials.cfm), 52 Pages, 2015	☐
	5	Allergan, Inc. 2003 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 52 Pages	☐
	6	Allergan, Inc. 2004 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 16 Pages	☐
	7	Allergan, Inc. 2006 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
	8	Allergan, Inc. 2005 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 35 Pages	☐
	9	Allergan, Inc. 2009 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
	10	Allergan, Inc. 2010 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 206 Pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	11	Allergan, Inc. 2011 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 174 Pages	☐
	12	Allergan, Inc. 2012 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	13	Allergan, Inc. 2013 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	14	American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology, 2013, 44 Pages	☐
	15	AUTRY, JILL ET AL, Mix It Up: When to Call a Compounding Pharmacist, Review of Optometry, July 15, 2012, 30-37, 149	☐
	16	Bausch and Lomb "Dry Eye Products," downloaded from Bausch and Lomb Website http://www.bausch.com/our-products/dry-eye-products/dry-eye-products, last accessed April 14, 2015, 2 Pages	☐
	17	Certain Ophthalmic Combination Drugs Containing a Steroid and Anti-Infective(s) for Human Use; Drug Efficacy Study Implementation; Amendment, Federal Register, 1982, 21296-21301, 47	☐
	18	Certain Steroid Preparations for Ophthalmic and/or Otic Use, Federal Register, 1976, 34340-34342, 41	☐
	19	CHANANA, GURMUKH ET AL, Particle Size Reduction of Emulsions By Formulation Design-II: Effect of Oil and Surfactant Concentration, PDA Journal of Pharmaceutical Science and Technology, 1995, 71-76, 49(2)	☐
	20	CHIDAMBARAM, N. ET AL, Effect of Nonionic Surfactant on Transport of Surface-Active and Non-Surface-Active Model Drugs and Emulsion Stability in Triphasic Systems, AAPS Pharmasci, 2000, 1-11, 2(3)	☐
	21	CHUNG, HESSON ET AL, Oil Components Modulate Physical Characteristics and Function of the Natural Oil Emulsions As Drug or Gene Delivery System, Journal of Controlled Release, 2001, 339-350, 71	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	22	COLES, WILLIAM ET AL, Dynamics of Ocular Surface pH, British Journal of Ophthalmology, 1984, 549-552, 68	☐
	23	CTFA Becomes the Personal Care Products Council, 1 Page, 2015 (http://www.personalcarecouncil.org/ctfa-becomes-personal-care-products-council)	☐
	24	Curriculum Vitae of Christopher N. Ta, Ph.D., 23 Pages, 2015	☐
	25	Curriculum Vitae of Erning Xia, Ph.D., 17 Pages, 2015	☐
	26	Curriculum Vitae of Harry C. Boghigian, 11 Pages, 2015	☐
	27	DE PAIVA, C.S. ET AL, Rationale for Anti-Inflammatory Therapy in Dry Eye Syndrome, Arq. Bras. Oftalmol., 2008, 89-95, 71	☐
	28	Declaration of Christopher N. Ta, Ph.D., 57 Pages, 2015	☐
	29	Declaration of Erning Xia, Ph.D., 197 Pages, 2015	☐
	30	Declaration of Harry C. Boghigian, 37 Pages, 2015	☐
	31	Drugs@FDA: FDA Approved Drug Products, LACRISERT, downloaded from the FDA website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails, last accessed April 16, 2015, 2 Pages	☐
	32	Drugs@FDA: FDA Approved Drug Products, RESTASIS, downloaded from the FDA website http://www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm, last accessed April 14, 2015, 2 Pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	33	Dry Eye Drop Symptom Relief Product information at Systane.com, Systane Products, Systane Ultra Lubricant Eye Drops, downloaded from Alcon website http://www.systane.com/Dry-Eye-Drop.aspx, last visited April 21, 2015, 2 Pages	☐
	34	FREEMAN, JERRE MINOR, The Punctum Plug: Evaluation of a New Treatment For The Dry Eye, Transactions American Academy of Ophthalmology and Otolaryngology, 1975, 874-879, 79	☐
	35	GILBARD, JEFFERY, Dry Eye, Blepharitis and Chronic Eye Irritation: Divide and Conquer, J Ophthalmic Nurs. Technol., 1999, 109-115, 18	☐
	36	GOTO, EIKI ET AL, Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction, Ophthalmology, 2002, 2030-2035, 109	☐
	37	INATOMI, TSUTOMU ET AL, Expression of Secretory Mucin Genes By Human Conjunctival Epithelia, Invest Ophthalmol Vis Sci, 1996, 1684-1692, 37	☐
	38	KUNERT, KATHLEEN ET AL, Analysis of Topical Cyclosporine Treatment of Patients With Dry Eye Syndrome, Arch Ophthalmol, 2000, 1489-1496, 118	☐
	39	Lacrisert (hydroxypropyl cellulose ophthalmic insert) Approved Label, downloaded from the FDA website http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/018771s0171bl.pdf, last accessed April 14, 2015, 7 Pages	☐
	40	Learn more about Systane Gel Drops at Systane.com, Systane Products, Systane Gel Drops, Downloaded From Alcon Website http://www.systane.com/Gel-Drops.aspx, last accessed April 21, 2015	☐
	41	LEMP, MICHAEL, Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, CLAO, 1995, 221-232, 21	☐
	42	LIU, KEVIN ET AL, Synthetic Approaches to the 2010 New Drugs, Bioorganic & Medicinal Chemistry, 2012, 1155-1174, 20	☐
	43	MAISSA, CECILE ET AL, Effect of Castor Oil Emulsion Eyedrops on Tear Film Composition and Stability, Contact Lens &Anterior Eye, 2010, 76-82, 33	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	44	MANN, ELAINE, Drugs Used in the Treatment of Dry Eye Syndrome, Anti-Inflammatory Drugs and Topical Anti-Allergy Drugs, Continuing Education & Training, 2007, 30-40	☐
	45	MURPHY, ROB ET AL, The Once and Future Treatment of Dry Eye, Review of Optometry January 2000 Cover Focus, 2000, 6 Pages (http://legacy.revoptom.com/archive/FEATURES/ro0200f6.htm)	☐
	46	NAPPER, G. ET AL, Ocular Therapeutics, Clin & Exp Optometry, 2003, 414-415, 86	☐
	47	Ophthalmic Drug Products for Over-The-Counter Human Use; Final Monograph, Federal Register, 1988, 7076-7093 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-theCounterOTCDrugs/StatusofOTCRulemakings/ucm071941.htm), 53	☐
	48	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, patent and exclusivity data for Restasis, downloaded from FDA website http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050790&Product_No=001&table1=OB_Rx, last accessed January 12, 2015	☐
	49	Personal Care Production Council (http://personalcarecouncil.org/) 3 Pages, 2015	☐
	50	PFLUGFELDER, STEPHEN ET AL, The Diagnosis and Management of Dry Eye: A Twenty-Five-Year Review, Cornea, 2000, 644-649, 19(5)	☐
	51	Restasis Approved Label, download from the Allergan Website (https://www.restasisprofessional.com/RestasisProfessional/FullPrescribingInformation) 6 Pages, 2015	☐
	52	ROWE, E.L., Effect of Emulsifier Concentration and Type on the Particle Size Distribution of Emulsions, Journal of Pharmaceutical Science, 1965, 260-264, 54	☐
	53	SOLOMON, ABRAHAM ET AL, Doxycycline Inhibition of Interleukin-1 in the Corneal Epithelium, Ophthalmol Vis Sci, 2000, 25544-2557, 41	☐
	54	Systane Lubricant Eye Drops Information at Systane.com, Systane Products, Systane Balance Lubricant Eye Drops, Download from Alcon Website http://www.systane.com/systane-Balance-Lubricant-Eye-Drops.aspx, last accessed April 21, 2015	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	55	Systane Lubricant Eye Gel, Systane Products, Systane Lubricant Eye Gel, Downloaded from Alcon Website http:// www.systane.com/systane-Lubricant-Eye-Gel.aspx, last visited April 21, 2015, 2 pages	☐
	56	TABAN, MEHRYAR ET AL, Update on Punctal Plugs, Comp. Ophthalmology Update, 2006, 205-2012, 7(5)	☐
	57	TURNER, KATHLEEN ET AL, Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion, Cornea, July 2000, 492-496, 19(4)	☐
	58	YEH, STEVEN ET AL, Apoptosis of Ocular Surface Cells in Experimentally Induced Dry Eye, Invest Ophthalmol Vis, 2003, 124-129, 44	☐
	59	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, pages 1 - 43, Dated September 18, 2015	☐
	60	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, pages 1 - 46, Dated September 17, 2015	☐
	61	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, pages 1 - 46, Dated September 17, 2015	☐
	62	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, pages 1 - 43, Dated September 22, 2015	☐
	63	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, pages 1 - 47, Dated September 18, 2015	☐
	64	In the United States District Court for the Eastern District of Texas Marshall Division, Allergan, Inc. (Plaintiff) v. Actavis, Inc., Watson Laboratories, Inc., and Actavis Pharma, Inc. (f/k/a Watson Pharma, Inc.) (defendants), C.A. No. 2:14-cv-638-JRG-Lead Case Consolidated with 2:14-cv-188-JRG, Actavis, Inc., Waston Laboratories, Inc., and Actavis Pharma, Inc.'s Invalidity Contentions Pursuant to Local Patent Rules 3-3 and 3-8, pages 1-74, dated October 15, 2014	☐
	65	Letter from Victor Ramsaywak of Apotex, Inc., Notice of Certification Under 21 USC Section 355(j)(2)(B)(ii) (Section 505(j)(2)(B(ii) of the Federal Food, Drug and Cosmetic Act(and 21 CFR Section 314.95 dated July 23, 2015, pages 1-116	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	66	Letter from Shashank Upadhye, Counsel for InnoPharma, Inc., of Amin Talati & Upadhye, Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Patent Nos. 5,474,979; 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, dated July 31, 2015, pages 1-98	☐
	67	Letter from J.C. Rozendaal of Kellogg, Huber, Hansen, Todd, Evans & Figel, PLLC, Notice of ANDA No. 203880 Concerning Cyclosporine Ophthalmic Emulsion, 0.05% with Paragraph IV Certification Concerning U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 dated July 22, 2015, pages 1-40	☐
	68	Letter from Joseph M. Reisman, Counsel for Mylan Pharmaceuticals Inc., of Knobbe Martens, Cyclosporine Emulsion 0.05%, Route of Administration: Ophthalmic, U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930, Notice of Paragraph IV Certification, dated July 20, 2015, pages 1-226	☐
	69	Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act - 21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated July 10, 2015, pages 1-26	☐
	70	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, Pages 1-63, Dated June 4, 2015	☐
	71	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, Pages 1-63, Dated June 4, 2015	☐
	72	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, Pages 1-63, Dated June 4, 2015	☐
	73	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, Pages 1-63, Dated June 4, 2015	☐
	74	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, Pages 1-63, Dated June 4, 2015	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-10-22
Name/Print	Laura L. Wine	Registration Number	68,681

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

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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.

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Ken Dinh
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	23869444
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	21:48:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	6642
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	17618C6C1-IDS3.pdf	600653 0a15927604b9a3954295772381e4365098d919d9	no	11
Warnings:					
Information:					
A U.S. Patent Number Citation is required in the Information Disclosure Statement (IDS) form. You may remove the form to add the required data in order to correct the Informational Message or if you chose not to, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Non Patent Literature	1-Albietz_2001.pdf	3086250 50def76539f42013897ffb8cd880d82fe460e420	no	15
Warnings:					
Information:					
3	Non Patent Literature	2-Allergan_Dry_Eye_Product_Portfolio_Fact_Sheet.pdf	70312 ac07a39d66c1f06292b6f83511cf5935a647fa4e	no	4
Warnings:					
Information:					
4	Non Patent Literature	3-2001AnnualReport.pdf	622863 82555bc7430c21949918c307600b143a2a3064ad	no	54
Warnings:					
Information:					
5	Non Patent Literature	4-2002AnnualReport.pdf	669071 f90755e0380463234eb18d279d10eb11a5e225f8	no	52
Warnings:					
Information:					
6	Non Patent Literature	5-2003AnnualReport.pdf	1435223 fc753e3d8ea3d7133253bd3dd965951b88b74945	no	52
Warnings:					
Information:					
7	Non Patent Literature	6-2004AnnualReport.pdf	1638526 2481e32da0aa61213712119cbf8e544956e6f79e	no	16
Warnings:					

Information:					
8	Non Patent Literature	10-Allergan_2010_Annual_Report.pdf	1496428 63b44b786bcf2b5209af0003bf65ef8393766f7e	no	206
Warnings:					
Information:					
9	Non Patent Literature	11-2011AnnualReport.pdf	1871227 f16fccf5f278dca24b81cb0a9faeb01cac2be50e	no	174
Warnings:					
Information:					
10	Non Patent Literature	13-2013AnnualReport.pdf	810452 dc38bfc59b4057874fd3933763fc6be7324ca4eb	no	28
Warnings:					
Information:					
11	Non Patent Literature	14-AAO_Preferred_Practice_Guidelines.pdf	4345179 40e675925c4688b2ac3472048bf691ee427065e4	no	44
Warnings:					
Information:					
12	Non Patent Literature	15-Autry_2012.pdf	1458466 fbe949276b45b256fb9d5eb6a5fbee3c4f28b542	no	7
Warnings:					
Information:					
13	Non Patent Literature	16-Bausch_Lomb_Dry_Eye_Products.pdf	112607 944920bd7aba364a5081eaab6abdf79fb5a2ed68	no	2
Warnings:					
Information:					
14	Non Patent Literature	17-Fed_Reg_1982.pdf	2305147 9944f6fbf76d4ac59961537b1af19cd93ccf1cd6	no	6
Warnings:					
Information:					
15	Non Patent Literature	18-Fed_Reg_1976.pdf	1200642 cdfee77011f2ae7c9eb741accf9891c9c23255b0	no	3
Warnings:					
Information:					
16	Non Patent Literature	19-Chanana_1995.pdf	1328772 ab75943df6278dfc9d7546a3144b1951881080ae	no	8
Warnings:					

Information:					
17	Non Patent Literature	20-Chidambaram_2000.pdf	186053 ed4cdb1d837de5c6f49e61fc6540821379a4b6b2	no	11
Warnings:					
Information:					
18	Non Patent Literature	21-Chung_2001.pdf	1828298 0bbc80a579ffe1353b592fae3dc830dc8829604f	no	14
Warnings:					
Information:					
19	Non Patent Literature	22-Coles-1984.pdf	782868 193d4b8f65e31eb4c15f1ceea26ca86427dfe985	no	4
Warnings:					
Information:					
20	Non Patent Literature	23-ctfa-becomes-personal-care.pdf	48099 22d04d5378543d3e6a05706475fab034c0f961ef	no	1
Warnings:					
Information:					
21	Non Patent Literature	24-Ta2015.pdf	126419 69d94ab648acf144914af4460adf733aef011c78	no	23
Warnings:					
Information:					
22	Non Patent Literature	26-Boghigian2015.pdf	67933 3eb7c665d9963c4196732d48971d60e2ac0f8c8f	no	11
Warnings:					
Information:					
23	Non Patent Literature	27-DePaiva_2008.pdf	82792 4dd317bda060d2e3a5fab7d173fd19f673ac86f3	no	7
Warnings:					
Information:					
24	Non Patent Literature	28-Declaration_of_Christopher_Ta.pdf	898978 9e1393cfaefb26b69e2ea0186a662d73e8d00249	no	57
Warnings:					
Information:					
25	Non Patent Literature	29-Declaration_of_Erning_Xia.pdf	570041 bebbf4b177c6267d4da99f81059013e375e1e194	no	197
Warnings:					

Information:					
26	Non Patent Literature	30-Declaration_of_Harry_Boghigian.pdf	224119 26ed7ad7ccad4ce900b34731180ae4301b76b8d4	no	37
Warnings:					
Information:					
27	Non Patent Literature	31-DrugsFDA-FDA_Approved_Drug_Products-Lacrisert.pdf	98132 6145010b412ba090a1adb5a2c38bc57fed2a9fb7	no	2
Warnings:					
Information:					
28	Non Patent Literature	32-DrugsFDA_Restasis_NDA_Number.pdf	101335 23b87c74ebc2c9824417bbc6149ba031f564678a	no	2
Warnings:					
Information:					
29	Non Patent Literature	33-SYSTANE_ULTRA.pdf	106040 823fbe353fc5d79cec671d1f6f5fec155aa8f569	no	2
Warnings:					
Information:					
30	Non Patent Literature	34-Freeman-1975.pdf	824096 6a0aef77358c1a0236a2459414356893ac1d1f43	no	8
Warnings:					
Information:					
31	Non Patent Literature	35-Gilbard_1999.pdf	1655617 f6f2caf10750806b760b2c156165f3b416fb0b50	no	7
Warnings:					
Information:					
32	Non Patent Literature	36-Goto_2002.pdf	131711 f118c0ed202e33ce6c6c4e8641fe033dfa1a3635	no	6
Warnings:					
Information:					
33	Non Patent Literature	37-Inatomi_1996.pdf	4043479 90c60e29866ca1cf9c9582e388d7185d3adb1f79	no	9
Warnings:					
Information:					
34	Non Patent Literature	38-Kunert-2000.pdf	1887798 974d5e8ea565c925d6defa8f1383185ed95d040a	no	10
Warnings:					

Information:					
35	Non Patent Literature	39-Lacrisert_Approved_Label.pdf	342990 1049556890ec281e28e0475c24d9e48f737cdb5b	no	7
Warnings:					
Information:					
36	Non Patent Literature	40-SYSTANE_Gel_Drops.pdf	98965 7389705040af0e40b894e60462a1b935eca30c93	no	2
Warnings:					
Information:					
37	Non Patent Literature	41-Lemp_1995.pdf	1419730 39bb26b9613ef12397b9063618d2a61b5eca9317	no	12
Warnings:					
Information:					
38	Non Patent Literature	42-Liu_2012.pdf	304884 6b4ba660cc8a3dc8b34ed40431bfb1a749c79368	no	20
Warnings:					
Information:					
39	Non Patent Literature	43-Maissa_2010.pdf	284313 2e7733b3e6ccac79cad7e4a46f9889bd809db929	no	7
Warnings:					
Information:					
40	Non Patent Literature	44-Mann_2007.pdf	198950 78d259ce8a334eb16f13bfb7b56ba4741623e10a	no	11
Warnings:					
Information:					
41	Non Patent Literature	45-Murphy_2000.pdf	79641 cddaac123030af8c12d48986f8a9cde5cf68666f	no	6
Warnings:					
Information:					
42	Non Patent Literature	46-Napper_2003.pdf	546635 1745a8af25371d2fc3faef0c68bca3c5f1d73e80	no	2
Warnings:					
Information:					
43	Non Patent Literature	47-Federal_Register_1988.pdf	9149292 308bcd9f4144f17d323dfaf70571e8bbcb6e5cd9	no	18
Warnings:					

Information:					
44	Non Patent Literature	48-Orange_Book_Patent_and_Data.pdf	68334 c0b3938f56bcd0d7a34dae786500428534f7f561	no	1
Warnings:					
Information:					
45	Non Patent Literature	49-personalcarecouncil_website.pdf	99997 fbb3fe369b01086a8ced448f6aa89083597bd8bc	no	3
Warnings:					
Information:					
46	Non Patent Literature	50-Pflugfelder_2000.pdf	112022 0dfb43502893ccc8b086cb4788d0493eebad9c9e	no	6
Warnings:					
Information:					
47	Non Patent Literature	51-Restasis_label.pdf	88958 14ba58133ee6f63ad4358d64560397b7b84ba8ce	no	6
Warnings:					
Information:					
48	Non Patent Literature	52-Rowe_EL_1965.pdf	1095627 ae274ce76151760bb46d272a1badfbf4027c61d2	no	6
Warnings:					
Information:					
49	Non Patent Literature	53-Solomon_2000.pdf	257458 46b710c7928f70bd8bddc3b8cd1909b7c3430ff5	no	14
Warnings:					
Information:					
50	Non Patent Literature	54-SYSTANE_BALANCE.pdf	104274 4c5a896d13ea984a5bb40eae5329fcf10f9ab76c	no	2
Warnings:					
Information:					
51	Non Patent Literature	55-SYSTANE_Lubricant_Eye_Gel.pdf	101250 1d32d73825a29d45f088ab33185ac7f85dbc0d70	no	2
Warnings:					
Information:					
52	Non Patent Literature	56-Taban_2006.pdf	3615485 b002171ab25af0ec194606a31a2106fc54fbacd0	no	8
Warnings:					

Information:					
53	Non Patent Literature	57-Turner_2000.pdf	571723 8e39345486c360b4292fb7fc2d3975499074bc98	no	7
Warnings:					
Information:					
54	Non Patent Literature	58-Yeh_2003.pdf	252635 3edd0311574249121e7bcd955e56d97b7597ec37	no	6
Warnings:					
Information:					
55	Non Patent Literature	59-IPR2014-01278-Patent-Owner-Preliminary-Response.pdf	151071 c6615c65e163c80c18123179ea4c97b50e227dff	no	43
Warnings:					
Information:					
56	Non Patent Literature	60-IPR2015-01282-Patent-Owner-Preliminary-Response.pdf	144350 49f0f2b408cbeee37f76e3fab0a5b71bf3ac0999	no	46
Warnings:					
Information:					
57	Non Patent Literature	61-IPR2015-01283-Patent-Owner-Preliminary-Response.pdf	145110 500f7a0ca7147172185bdff761ba1bac22e74684	no	46
Warnings:					
Information:					
58	Non Patent Literature	62-IPR2015-01284-Patent-Owner-Preliminary-Response.pdf	151362 695bd029ed182b10921aa46b32456d4c33496f18	no	43
Warnings:					
Information:					
59	Non Patent Literature	63-IPR2015-01286-Patent-Owner-Preliminary-Response.pdf	160103 88315e8d187dce82952194bc105d05187717a9bb	no	47
Warnings:					
Information:					
60	Non Patent Literature	64-Defs_Invalidity_Contentions_2014-10-15.pdf	287871 401c1ab15244eb7209fee29c2b5c38cfc0ddc92e	no	74
Warnings:					
Information:					
61	Fee Worksheet (SB06)	fee-info.pdf	30785 31f8eef446de50351b0e0b1be9895084f40e0dbd	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	56579441

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 08/20/2015

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

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
08/20/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

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

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

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

Date of Interview: *8/14/2015*.

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: *37-63*.

Identification of prior art discussed: *Sall et al. (Ophthalmology, 2000)*.

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...)

Applican'ts representative discussed the support for the claims, mentioning pages 3-4. Examiner indicated that pointing this section in the response to the new matter rejection of record would be helpful. Additional, inclusion of Example 1 which has the components of the compositions within the claimed methods was suggested by Examiner. No agreement was reached. Applicant's representative plans to follow up with a written response.

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 1676	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

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

MAILED
JUN 15 2015
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/222,478

1. THE REQUEST FILED May 26, 2015 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to **Michelle R. Eason** at (571) 272-4231. In his/her absence, calls may be directed to Brian W. Brown at (571) 272-5338.

/Michelle R. Eason/
(*Signature*)

Paralegal Specialist, Office of Petitions
(Title)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 06/10/2015

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

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
06/10/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/26/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

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

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/26/2015 has been entered.

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

Election/Restrictions

3. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

Status of the claims

4. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 37, 49 and 57 comprise the limitations Claim 37: "(…) wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporine A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (..)"

Claim 49 "(…) wherein the method is therapeutically effective in treating dry eye disease and wherein the method achieves at least as much therapeutic efficacy as administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (...)"

Claim 57 "(…) wherein the method demonstrates a reduction in adverse events in the human compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion comprising cyclosporine A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (…)"

New Matter

7. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

Lack of Ipsis verbis support

8. With respect to the limitations above, such embodiments does not appear to be expressly disclosed nor described in the Example 1.

Lack of Inherent support

9. "While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentrations is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

Applicants' arguments

10. The Applicants do not agree with the rejection, and respectfully submit that the Claims comply with the written description requirement for the reasons previously submitted to the Office. For example, support for the aforementioned limitation can be found, at least, in the paragraph at page 9, line 25 - page 10, line 7 of the specification as originally filed:

> The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. **Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.**

Specification filed March 21, 2014 at page 9, line 25 - page 10, line 7 (Emphasis Added).

Moreover, the Applicants further respectfully submit that the Claims comply with the written description requirement, at least, because the "at a frequency of twice a day" limitation is supported in the specification as required by MPEP § 2163. The Applicants submit that the written description clearly shows that the descriptive matter (the "twice a day" limitation) is present in the specification. Example 1 of the present application describes the testing of the 0.05% CsA and 0.1% CsA formulations (see present Application specification as filed, page 26, lines 1-21):

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I	Composition II
	wt%	wt%
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Purite®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The Applicants note that those formulations were disclosed to a person of skill in the art for the first time in the present application family, including US Patent Application No. 10/927,857 and Provisional US Patent Application No. 60/503,137. A person of skill in the art would not have known those formulations prior to the filing of the instant patent application family.

Upon learning the formulations of the compositions used in the Phase 3, double-masked, randomized, parallel group studies described in the application, a person of skill would have understood that the application was describing the Phase 3, double-masked, randomized, parallel group study described earlier in the specification:

In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. (...) "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eve disease. CsA Phase 3 Study Group," Sall et al., Ophthalmology, 2000 Apr, 107(4):631-9. See Present Application Specification as filed, page 1, line 21 - page 2, line 15. The abstract of Sall describes that the patients in the Phase 3 study received either a 0.05% CsA Formulation or 0.1% CsA Formulation at a frequency of twice a day (Sall, ABSTRACT):

Kenneth Sall, MD,[1] Owen Dean Stevenson, MD,[2] Thomas E. Mundorf, MD,[3] Dennis L. Bass, PhD[4] and the CsA Phase 3 Study Group

Objective: To compare the efficacy and safety of cyclosporin A [CsA] 0.05% and 0.1% ophthalmic emulsions to vehicle in patients with moderate to severe dry eye disease.
Design: Multicenter, randomized, double-masked, parallel-group, 6-month, vehicle-controlled.
Participants: A total of 877 patients with defined moderate to severe dry eye disease (292 to 293 in each treatment group).
Methods: Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis.

The Sall paper does not disclose the compositions of the formulations, and a person of skill in the art would not have known these formulations. Hence, the "twice a day" limitation is present in the present application and a person of skill's knowledge of the 0.05% CsA Phase 3 trial as disclosed in the Sall paper would lead them to understand that both the 0.05% CsA and 0.1% CsA formulations were dosed at a

frequency of twice a day. Thus, the Applicants submit that the "twice a day" limitation is properly supported and the claims satisfy the written description requirement.

Response to arguments

11. Applicant's arguments have been carefully considered but not deemed persuasive for the reasons of record and for the following reasons: According to MPEP 609.01 and 37 C.F.R. 1.57:

"Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:

(1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by 35 U.S.C. 112(a);

(2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by 35 U.S.C. 112(b); or

(3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by 35 U.S.C. 112(f).

In the instant case, Applicant's representative is incorporating essential subject matter (i.e., the instantly claimed wherein clauses as listed above in pages 3-4) by relying on a NPL reference (Sall, 2000) which was not expressly incorporated by reference, nor is it a U.S. Patent or a U.S. Patent Application as required by 37 CFR 1.57. Thus it is deemed that Applicants did not have possession of the invention as claimed. For these reasons, the new matter rejection of record is maintained.

Conclusion

13. No claim is currently allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. An obviousness rejection over Sall et al. (Ophthalmology, 2000, cited in the IDS dated 3/28/2014) in view of Ding et al. (US 5,474,979, cited in the IDS dated 3/28/2014) is not being made for the reasons summarized by Examiner in the Declarations under 37 CFR 1.132 and Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed out on 1/28/2014 for 13/961,828, of which the instant application is a continuation.

14. 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 1676

MMCG 06/2015

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG
EAST search (attached)	6/4/2015	MMCG
also ran PALM Inventor search	6/4/2015	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1137	polysorbate same acrylate same alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L2	90	polysorbate near3 acrylate same alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L3	37	polysorbate near3 acrylate near3 alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L4	9	polysorbate near3 acrylate near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L5	132	"polysorbate 80" and acrylate near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L6	7	"polysorbate 80" and acrylate near3 c10-30 Near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L7	185	"5474979"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:27

EAST Search History (Interference)

<This search history is empty>

6/4/2015 6:08:06 PM

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14222478	Filing Date	2014-03-21	Docket Number (if applicable)	17618-CON6CON1 (AP)	Art Unit	1676
First Named Inventor	Andrew Acheampong			Examiner Name	Codero Garcia, Marcela M.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 010885

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-05-26
Name	Laura L. Wine	Registration Number	68681

This collection of information is required by 37 CFR 1.114. 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 1.11 and 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, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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 the Freedom of Information Act requires disclosure of these records.

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 inspections 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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Andrew Acheampong	Nonprovisional Application Number (if known):	14222478
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Laura L. Wine/	Date May 26, 2015
Name (Print/Typed) Laura L. Wine	Practitioner Registration Number 68681

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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.

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO FINAL OFFICE ACTION DATED NOVEMBER 24, 2014

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

Dear Sir:

These papers are filed in reply to the final Office Action mailed November 24, 2014.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

Telephonic interviews were conducted on November 12 and 17, 2014 and were attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37, 49, and 57.

Principal Arguments and Other Matters

The rejection under 35 U.S.C. § 112, first paragraph was discussed. No substantive agreement was reached.

Results of Interview

It was understood that a final office action would be issued.

REMARKS

This Reply responds to the Final Office Action sent November 24, 2014, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement with regards to the limitation in Claims 37, 49, and 57 of "at a frequency of twice a day" within the following wherein clauses:

"(…) wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (..)"
Claim 37

"(…) wherein the method is therapeutically effective in treating dry eye disease and wherein the method achieves at least as much therapeutic efficacy as administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight(…)"
Claim 49

"(…) wherein the method demonstrates a reduction in adverse events in the human, compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion

comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight(…)"

Claim 57

The Applicants do not agree with the rejection, and respectfully submit that the Claims comply with the written description requirement for the reasons previously submitted to the Office. For example, support for the aforementioned limitation can be found, at least, in the paragraph at page 9, line 25 – page 10, line 7 of the specification as originally filed.

Moreover, the Applicants further respectfully submit that the Claims comply with the written description requirement, at least, because the "at a frequency of twice a day" limitation is supported in the specification as required by MPEP § 2163.

The Applicants submit that the written description clearly shows that the descriptive matter (the "twice a day" limitation) is present in the specification. Example 1 of the present application describes the testing of the 0.05% CsA and 0.1% CsA formulations:

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I	Composition II
	wt%	wt%
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

Present Application Specification as filed, page 26, lines 1-21.

The Applicants note that those formulations were disclosed to a person of skill in the art for the first time in the present application family, including US Patent Application No. 10/927,857 and Provisional US Patent Application No. 60/503,137. A person of skill in the art would not have known those formulations prior to the filing of the instant patent application family.

Upon learning the formulations of the compositions used in the Phase 3, double-masked, randomized, parallel group studies described in the application, a person of skill would have understood that the application was describing the Phase 3, double-masked, randomized, parallel group study described earlier in the specification:

> In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. (…) "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group," Sall et al, *Ophthalmology, 2000 Apr, 107(4):631-9*.

See Present Application Specification as filed, page 1, line 21 – page 2, line 15.

The abstract of Sall describes that the patients in the Phase 3 study received either a 0.05% CsA Formulation or 0.1% CsA Formulation at a frequency of twice a day:

Kenneth Sall, MD,[1] Onex Dana Stevenson, MD,[2] Thomas K. Mundorf, MD,[3] Brenda L. Reis, PhD[4] and the CsA Phase 3 Study Group

Objective: To compare the efficacy and safety of cyclosporin A ([CsA] 0.05% and 0.1% ophthalmic emulsions) to vehicle in patients with moderate to severe dry eye disease.
Design: Multicenter, randomized, double-masked, parallel-group, 6-month, vehicle-controlled.
Participants: A total of 877 patients with defined moderate to severe dry eye disease (292 to 293 in each treatment group).
Methods: Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis.

Sall, ABSTRACT. The Sall paper does not disclose the compositions of the formulations, and a person of skill in the art would not have known those formulations.

Hence, the "twice a day" limitation is present in the present application and a person of skill's knowledge of the 0.05% CsA Phase 3 trial as disclosed in the Sall paper would lead them to understand that both the 0.05% CsA and 0.1% CsA formulations were dosed at a frequency of twice a day. Thus, the Applicants submit that the "twice a

day" limitation is properly supported and the Claims satisfy the written description requirement.

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Conclusion

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: May 26, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**6600**

Electronic Acknowledgement Receipt

EFS ID:	22449941
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	26-MAY-2015
Filing Date:	21-MAR-2014
Time Stamp:	18:30:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6600
RAM confirmation Number	9350
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	17618CON6CON1_RCE.PDF	697619 4f1401512339bb0638516ba40f5304f757c0e19d	no	3
Warnings:					
Information:					
2		17618CON6CON1_Response_05-26-2015.pdf	730195 a241f4316df503c303469bd0388201f6eedd5ea7	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
TrackOne Request	1	2
Response After Final Action	3	3
Applicant summary of interview with examiner	4	4
Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	34286 128098f4342a56017c699f6d1495d0796a7e2e2a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1462100		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 11/24/2014

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

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
11/24/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

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

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

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

Date of Interview: *12 November 2014*.

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: *37,49,53 and 57*.

Identification of prior art discussed: *N/A*.

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...)

Discussed the limitation"twice a day" within the claim limitation "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight". Applicants' arguments were not persuasive with respect to the rejection of record because the unexpected results described in the disclosure (e.g., Example 1) are not limited to twice a day administration (see attached Office Action). Applicant's representative requested a written office action in a telephonic conversation on 11/17/2014.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of 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 1676	

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/25/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *7/8/2014*.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20141106* .

4) ☐ Other: _____.

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

DETAILED ACTION

2. This Office Action is in response to the reply received on 9/25/2014.

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

Election/Restrictions

3. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

Status of the claims

4. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 37, 49 and 57 comprise the limitation "at a frequency of twice a day", specifically in the wherein clause defining the unexpected results, i.e., "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight".

New Matter

7. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

Lack of Ipsis verbis support

8. With respect to the limitation “at a frequency of twice a day” in the wherein clause “wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1%

by weight of castor oil in an amount of about 1.25 % by weight", such embodiment does not appear to be expressly disclosed nor described in the Example 1. Furthermore, the limitation "at a frequency of twice a day" does not appear to be expressly disclosed with respect to the unexpected results described in claims 37, 49, 53 and 57 (as described in the respective wherein clauses). Note that in all the independent claims an unexpected result is described that depends on the "twice a day" administration. However, the disclosure and the examples do not require this "twice a day" limitation for the unexpected results as claimed.

Lack of Inherent support

9. "While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentrations is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

Applicants' arguments

10. The Applicants submit that the currently pending Claims contain sufficient written description support for the "at a frequency of twice a day" limitation within the specification of the present application as originally filed. For example, support for this limitation can be found, at least, in the paragraph at page 9, line 25 - page 10, line 7 of the specification as originally filed, which reads:

> The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. **Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.**

Specification filed March 21, 2014 at page 9, line 25 - page 10, line 7 (Emphasis Added).

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Response to arguments

11. Applicants' arguments have been carefully considered and deemed persuasive for the generic method, i.e., lines 1-5 of claim 37, but not deemed persuasive for the unexpected results set forth in the wherein clause of claim 37 for the following reasons: With respect to the limitation “at a frequency of twice a day” in the wherein clause “wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight”, such embodiment does not appear to be expressly disclosed nor described in the Example 1. Furthermore, the limitation “at a frequency of twice a day” does not appear to be expressly disclosed with respect to the unexpected results described in independent claims 49, 53 and 57 (as described in the respective wherein clauses) for analog reasons as those set forth in claim 37. Note that in all the independent claims an unexpected result is described that requires "twice a day" administration. However, the disclosure and the examples do not require this "twice a day” limitation for the unexpected results as claimed.

"While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentration range for the claimed unexpected results is silent with regards to the frequency of administration.

Thus it is deemed that Applicants did not have possession of the invention as claimed, and therefore the new matter rejection is maintained.

Terminal disclaimers

12. Terminal disclaimers for US 8,685,930; 8,648,048; 8,642,556; 8,633,162 and 8,629,111 have been received and approved, thus obviating the ODP rejections of record.

Conclusion

13. No claim is currently allowed.

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

14. 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 1676

MMCG 11/2014

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

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

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

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

Date of Interview: *12 November 2014*.

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: *37,49,53 and 57*.

Identification of prior art discussed: *N/A*.

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...)

Discussed the limitation"twice a day" within the claim limitation "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight". Applicants' arguments were not persuasive with respect to the rejection of record because the unexpected results described in the disclosure (e.g., Example 1) are not limited to twice a day administration (see attached Office Action). Applicant's representative requested a written office action in a telephonic conversation on 11/17/2014.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of 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 1676	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

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

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4347238		1982-08-31	Hollingsbee	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2222770	GB	A	1990-03-21	Sandoz Ltd		☐
	2	198901772	WO	A1	1989-03-09	University of Georgia Research Foundation, Inc.		☐
	3	199318752	WO	A1	1993-09-30	Pharmos Corp.		☐

Receipt date: 07/08/2014	Application Number	14222478 14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

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

	4	0558906	JP	A	1993-03-09	Sankyo Co.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Marcela Cordero Garcia/	Date Considered	10/10/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Receipt date: 07/08/2014	Application Number	14222478 14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2014-07-08
Name/Print	Laura L. Wine	Registration Number	68681

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

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	421	cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36
L2	47	cyclosporin same castor and "1.5" near10 "0.5"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36
L3	31	cyclosporin same castor and "1.25" near10 "0.05"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	9	cyclosporin same castor and "1.25" near10 "0.05"	USPAT; UPAD	ADJ	ON	2014/11/06 16:00

11/6/2014 4:00:56 PM
C:\Users\mgarcia\Documents\EAST\Workspaces\12347683.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14222478
Filing Date	21-Mar-2014
First Named Inventor	Andrew Acheampong
Attorney Docket Number	17618CON6CON1 (AP)
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Allergan, Inc.	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

8685930

8648048

8642556

8633162

8629111

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

( ) Small Entity

( ) Micro Entity

(●) Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were 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 patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 68681

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

( ) A joint inventor; all of whom are signing this request

Signature	/Laura L. Wine/
Name	Laura L. Wine

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14222478

Filing Date: 21-Mar-2014

Applicant/Patent under Reexamination: Acheampong et al.

Electronic Terminal Disclaimer filed on September 25, 2014

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	20246997
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	25-SEP-2014
Filing Date:	21-MAR-2014
Time Stamp:	16:22:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	2933
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	35317 0120546a576347d21f62d6fb53c0006845527467	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30289 6b6345ed2c8b85fd47cf1c0d708505fff7797f99	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65606		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO NON-FINAL OFFICE ACTION DATED JUNE 25, 2014

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

Dear Sir:

These papers are filed in reply to the non-final Office Action mailed June 25, 2014.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

Remarks begin on page 2 of this paper.

REMARKS

This Reply responds to the Office Action sent June 25, 2014, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement with regards to the limitation in Claims 37, 49, and 57 of "at a frequency of twice a day".

The Applicants submit that the currently pending Claims contain sufficient written description support for the "at a frequency of twice a day" limitation within the specification of the present application as originally filed. For example, support for this limitation can be found, at least, in the paragraph at page 9, line 25 – page 10, line 7 of the specification as originally filed, which reads:

> The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. **Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand**.

Specification filed March 21, 2014 at page 9, line 25 – page 10, line 7 (Emphasis Added).

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Obviousness-Type Double Patenting Rejection

Claims 37-63 were rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 8,629,111. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 8,633,162. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 8,642,556. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 8,648,048. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,685,930.

While the Applicants do not agree with the non-statutory obviousness-type double patenting rejections recited above, in order to expedite prosecution, terminal disclaimers were filed on September 24, 2014 . Thus, the Applicants submit that the obviousness-type double patenting rejections have been rendered moot and request that the obviousness-type double patenting rejections be withdrawn.

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: September 25, 2014

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	20247409
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	25-SEP-2014
Filing Date:	21-MAR-2014
Time Stamp:	16:38:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON6CON1_Response_092514.pdf	117409 c2e9138ffcfcd9ed846e7072cb02de837abcc098	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	4
Warnings:			
Information:			
	Total Files Size (in bytes):	117409	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)

CONFIRMATION NO. 9616

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

PUBLICATION NOTICE

OC000000069795556

Title:METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Publication No.US-2014-0206626-A1
Publication Date:07/24/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	Cordero Garcia, Marcela M.
Attorney Docket Number	17618 CON6CON1 (AP)

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4347238		1982-08-31	Hollingsbee	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2222770	GB	A	1990-03-21	Sandoz Ltd		☐
	2	198901772	WO	A1	1989-03-09	University of Georgia Research Foundation, Inc.		☐
	3	199318752	WO	A1	1993-09-30	Pharmos Corp.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

	4	0558906	JP	A	1993-03-09	Sankyo Co.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	Cordero Garcia, Marcela M.
Attorney Docket Number	17618 CON6CON1 (AP)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2014-07-08
Name/Print	Laura L. Wine	Registration Number	68681

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

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 the Freedom of Information Act requires disclosure of these record s.

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 inspections 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.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number:
A61K 9/00, 9/08, 37/02	A1	WO 89/ 01772
		(43) International Publication Date: 9 March 1989 (09.03.89)

(21) International Application Number: PCT/US88/03039

(22) International Filing Date: 31 August 1988 (31.08.88)

(31) Priority Application Numbers: 092,466
117,218
187,823

(32) Priority Dates: 3 September 1987 (03.09.87)
4 November 1987 (04.11.87)
29 April 1988 (29.04.88)

(33) Priority Country: US

(71) Applicant: UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. [US/US]; Boyd Graduate Studies Center, Athens, GA 30602 (US).

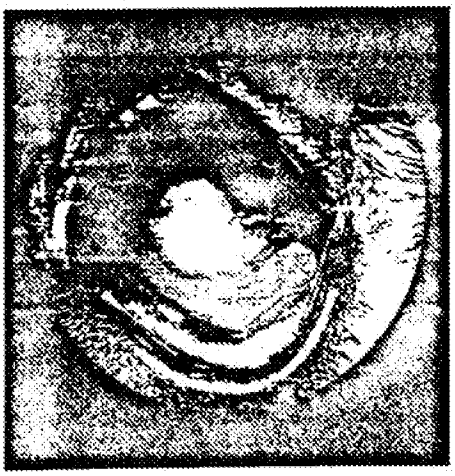
(72) Inventor: KASWAN, Renee ; 165 Snapfinger Drive, Athens, GA 30605 (US).

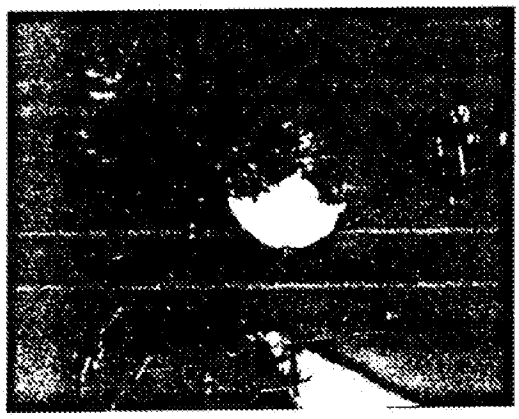
(74) Agent: PABST, Patrea, L.; Kilpatrick & Cody, 100 Peachtree Street, Suite 3100, Atlanta, GA 30043 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OCULAR CYCLOSPORIN COMPOSITION





(57) Abstract

A method for enhancing or restoring lacrimal function by the topical administration of a cyclosporin in a pharmaceutically acceptable excipient. Lacrimal function is enhanced or restored in patients suffering from abnormalities of the tear film including an absolute or partial deficiency in aqueous tear production, called keratoconjunctivitis sicca or KCS, regardless of etiology, including autoimmune dysfunction of the lacrimal glands. The treatment is also useful in the enhancement or restoration of normal tear production, and normal healing of the surface of the eye. The preferred composition for topical administration to the eye consists of cyclosporin dissolved in corn oil. The composition may further include antioxidants, lubricants, antibiotics, antifungals, antivirals, pilocarpine, vasoconstrictors, surfactants, wetting agents, anti-inflammatory agents (i.e. corticosteroids), preservatives, mucolytic agents (i.e. bromhexine, acetylcysteine), as well as other compounds. The most preferred composition is 2% cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben in corn oil.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America
FI	Finland	MG	Madagascar		

OCULAR CYCLOSPORIN COMPOSITION

The present invention relates to a method and composition for increasing tear production by the topical administration of cyclosporin to the patient's eyes.

BACKGROUND OF THE INVENTION

The exposed part of a normal eye is covered by a continuous thin tear film which is important for the well-being of the corneal and conjunctival epithelium and provides the cornea with an optically high quality surface. In addition, the aqueous part of the tear film acts as a lubricant to the eyelids during blinking of the lids. Certain enzymes contained in the tear fluid, for example immunoglobulin A, lysozyme and beta lysin, also have bacteriostatic properties.

The lacrimal apparatus consists of the secretory system (the source), the distribution system and the excretory system (the sink). In the secretory system, the bulk of the tear film, the aqueous tears, are supplied by the main and accessory lacrimal glands. The continuous production and drainage of aqueous tears is important in maintaining the corneal and conjunctival epithelium in a moist state, in providing nutrients for epithelial respiration, in supplying bacteriostatic agents and in cleaning the ocular surface by the flushing action of tear movement.

Abnormalities of the tear film include an absolute or partial deficiency in aqueous tear production, called keratoconjunctivitis sicca or KCS. In relatively mild cases, the main symptom of KCS is a foreign body sensation or a mild "scratchiness". This can develop into a constant, intense burning or

irritative sensation which can be debilitating to the patient. More severe forms lead to the development of filamentary keratitis, a painful condition characterized by the appearance of numerous strands or filaments attached to the corneal surface. Recent evidence suggests that these filaments represent breaks in the continuity of the normal corneal epithelial cells. The shear created by lid motion pulls these filaments, causing pain. Management of this stage of KCS is very difficult.

A frequent complication of KCS is secondary infection. Several breakdowns in the eye's normal defense mechanism seem to occur, presumably attributable to a decrease in the concentration of antibacterial lysozyme in the aqueous tears of a patient suffering from KCS.

Although KCS can develop in the absence of any other overt systemic abnormality, there is a frequent association of KCS with systemic disease. KCS can occur as part of a larger systemic involvement known as Sjogren's syndrome which is characterized by dry eyes, dry mouth, and arthritis.

Histologically in KCS (as part of Sjogren's syndrome or in isolation), the initial changes seen in the lacrimal gland are those of focal lymphocytic and plasma cell infiltrates associated with degeneration of glandular tissue. These changes resemble those seen in autoimmune disease in other tissue, giving rise to the speculation that KCS has an autoimmune basis.

Sjogren's syndrome is recognized as an exocrine glad dysfunction. Characteristically, the lacrimal glands show a mononuclear-cell infiltration that

ultimately leads to destruction of the glandular structure.

Conventional treatment of KCS is symptomatic. Normally, aqueous-deficient dry eye states are treated by supplementation of the tears with artificial tear substitutes. However, relief is limited by the retention time of the administered artificial tear solution in the eye. Typically, the effect of an artificial tear solution administered to the eye dissipates rapidly, within about thirty to forty-five minutes. The effect of such products, while soothing initially, does not last long enough. The patient is inconvenienced by the necessity of repeated administration of the artificial tear solution in the eye as needed to supplement the normal tears. Moreover, such treatment merely acts to alleviate the symptoms of the dry eye state and does not cure any underlying disorders or causes of the dry eye state.

The systemic use of corticosteroids has been advocated to treat these conditions. However, the merit of systemic corticosteroids in dry eye states has not been established. In most dry eye cases the hazards of long-term use of antiinflammatory agents would seem to outweigh their potential merit. It has also been suggested to administer orally a dilute solution of pilocarpine to stimulate the autonomic nervous system to effect increased aqueous tear production. This method of treatment has not met with universal favor because of the unpleasant side effects of ingested pilocarpine.

Surgical procedures have also been suggested in the management of dry eye states. Where there has been significant conjunctival destruction, mucous

membrane transplants have been advocated. It has also been suggested that parotid (saliva) duct transplantation can be useful in the management of dry eyes. However, since surgical alterations to combat dry eye conditions constitute such a drastic remedy and the benefit resulting from these alterations is questionable, these methods are usually used only as a last resort.

Cyclosporin is a metabolite isolated from the culture broths of the fungal species Tolypocladium inflatum Gams. A neutral, hydrophobic cyclic peptide composed of eleven amino acid resides, cyclosporin includes a previously unknown N-methylated amino acid composed of nine carbon atoms. Wenger, Synthesis of Cyclosporin and Analogues, pp. 14-25 in Cyclosporin A 1, Grune & Stratton, Inc. (New York 1983). A number of additional cyclosporins (B, C, D, E, and G) have been reported since the first cyclosporin was isolated (CsA). As described in U.S. Patent No. 4,117,118 issued September 26, 1978 to Harri et al., cyclosporin is readily soluble in most of the usual organic solvents and practically insoluble in petroleum ether and water. As distributed by Sandoz Ltd., Basel, Switzerland, under the tradename Sandimmune, cyclosporin for oral administration is dissolved in olive oil for further dilution with food and in polyoxyethylated castor oil and ethanol for intravenous injection.

Cyclosporin A was first proposed for use as an antifungal agent, but its immunosuppressive effects were found to be more marked than its antifungal potential. A potent immunosuppressive agent, cyclosporin is used to prolong survival of allogeneic

transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine and lung. The exact mechanism of action is not known but experimental evidence suggests that the effectiveness of cyclosporin is due to specific and reversible inhibition of immunocompetent cells, primarily T-helper cells. Lymphokine production, gamma interferon production and release of interleukin-2 or T-cell growth factor are also inhibited by cyclosporin.

Cyclosporin's immunosuppressive properties have led to its use in immune system related diseases. For example, U.S. Patent No. 4,649,047 describes a method for the treatment of phacoanaphylactic endophthalmitis and uveitis in the anterior or posterior segment of an eye wherein cyclosporin is topically administered to the eye. In other ophthalmic applications, cyclosporin has been used topically only for the treatment of external (e.g., corneal) eye diseases.

BenEzra et al., Amer. J. Ophthalmol. 101: 278-282 (1986), describe the effect of 2% cyclosporin eyedrops on severe vernal keratoconjunctivitis. Severe vernal keratoconjunctivitis is a seasonal allergic disorder unrelated to tear deficiency.

Hunter et al., Clin. Exp. Immunol. 45: 173-177 (1981) describe the topical administration of cyclosporin in a rabbit model of corneal graft rejection with positive results.

Boisjoly et al., Arch. Ophthalmol. 102: 1804-1807 (1984), have reported that topical application of cyclosporin had a beneficial prophylactic effect towards the treatment of severe herpetic stromal keratitis.

Mosteller et al., Investigative Ophthalmol. Supp. 25, 3: 38 (1984), disclose treating corneal allograft rejection in rabbits by applying a single dose of a 10% Cyclosporin A ointment in the lower cul-de-sac of the eyelids.

Cyclosporin has also been used systemically in other ophthalmic applications, where the disease being treated is not limited to the eye surface. For example, Nussenblatt et al., Amer. J. Ophthalmol. 96: 275-282 (1983), have reported clinical improvement in some patients with noninfectious posterior uveitis following systemic treatment with cyclosporin.

Cyclosporin is primarily administered orally or by injection. Unfortunately, cyclosporin used systemically has been associated with a high incidence of renal toxicity (kidney failure), some cases of hepatotoxicity, increased incidence of lymphoid tumors and increased incidence of opportunistic infections. Cyclosporin is only slightly less toxic than other immunosuppressive agents such as cytoxan or aziothioprine. The systemic side effects of cyclosporin are so severe and so common that they limit its use to life-threatening or in some cases severe sight-threatening disease. Finally, systemic application of cyclosporin is limited by its prohibitive cost.

As described in U.S. Patent No. 4,649,047 issued March 10, 1987 to Kaswan, topical administration of cyclosporin is useful in the treatment of a variety of immune mediated disorders of the eye, including uveitis and phacoanaphylactic endophthalmitis. This is also the preferred mode of administration to avoid

the undesirable side effects and cost of systemic administration.

To date, there has been no suggestion to treat a glandular dysfunction, a lacrimal gland dysfunction or an aqueous-deficient dry eye state with a cyclosporin, either topically or systemically.

Although cyclosporin has been topically administered in a variety of vehicles including arachis oil, a commercially available ointment base, and castor oil, the conventional carrier is olive oil. Unfortunately, topical administration of cyclosporin in olive oil to the eye of either humans or dogs is frequently accompanied by a burning sensation, pain, and redness. In some cases, other side effects have been observed including lid edema and periocular alopecia (hair loss around the eye). Similar problems have occurred with topical ophthalmic use of cyclosporin in the other vehicles. Studies have now demonstrated that these unpleasant side effects are due to the carrier, not to the cyclosporin. Unfortunately, cyclosporin is of very limited solubility and the number of acceptable carriers for ophthalmic use is limited.

It is therefore an object of this invention to provide a method of increasing tear production for a normal or tear-deficient eye, regardless of cause.

It is another object of this invention to provide a cyclosporin-based treatment of lacrimal gland dysfunction without the accompanying adverse physiological responses and economic difficulties associated with systemic cyclosporin treatments.

It is another object of the present invention to provide a composition containing an effective

concentration of cyclosporin for topical ophthalmic use which does not cause burning, redness or irritation.

It is a still further object of the present invention to provide a composition for topical ophthalmic use which is stable upon storage.

It is still another object of the present invention to provide a composition for topical ophthalmic use which promotes normal healing of the epithelial surface of the eye.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating a dry eye state in a patient by administering a cyclosporin topically to the patient's eye. The treatment is useful regardless of the cause of the dry eye, and includes treatment of autoimmune dysfunction of the lacrimal glands. The treatment is also useful in the enhancement or restoration of normal tear production, and normal healing of the surface of the eye.

The preferred composition for topical administration to the eye consists of cyclosporin dissolved in corn oil. The composition may further include antioxidants, lubricants, antibiotics, antifungals, antivirals, pilocarpine, vasoconstrictors, surfactants, wetting agents, anti-inflammatory agents (i.e. corticosteroids), preservatives, mucolytic agents (i.e. bromhexine, acetylcysteine), as well as other compounds.

The most preferred composition is 2%

cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben in corn oil.

Brief Description of the Drawings

Figure 1 is a graph demonstrating the effect of topical cyclosporin on lacrimination (STT mm/min) over time (days) in twelve normal male beagle dogs; following three days of baseline measurement with no treatment, six dogs were treated with 2% cyclosporin in olive oil applied topically two times daily, and six dogs were treated with placebo (olive oil) applied topically two times daily. The STT were determined twice daily in the cyclosporin treated dogs (■ ----- ▨) and in the olive oil treated dogs (▲ ---▲). Following 7 days all dogs were crossed over into the opposite treatment groups for an additional three days.

Figure 2 is a comparison of the appearance of the eye of a dog suffering from keratoconjunctivitis sicca before (Figure 2A) and after (Figure 2B) treatment for four weeks with 2% cyclosporin.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating tear-deficient dry eyes due to autoimmune disease or of unknown etiology which includes the step of administering a cyclosporin topically to the patient's eye. The invention includes a corn oil based cyclosporin composition which provides greatly enhanced benefits when applied topically to the eye over previous cyclosporin compositions.

Despite the apparent similarities in chemical structure, studies demonstrate the significant differences in comfort and incidence of side effects between cyclosporin in previously described carriers such as olive oil and cyclosporin in corn oil, both with and without preservative and antioxidant. These studies also establish that topically applied cyclosporin can be used to promote or effect normal healing and prevent or reverse scar formation on the ocular surface.

In accordance with the present invention, the cyclosporin may be used in any efficacious concentration, e.g., 0.01 to saturation (e.g., up to 50 weight percent of a cyclosporin) in a pharmaceutically acceptable excipient. Concentrations of 1.1 to 20 weight percent of a cyclosporin are preferred. Although the preferred vehicle is corn oil, as described below, other pharmaceutically acceptable excipients are, for example, animal oil, vegetable oil, appropriate organic or aqueous solvents, artificial tear solutions in which the cyclosporin is soluble, and natural or synthetic polymers or appropriate membranes.

Examples of these pharmaceutically acceptable excipients are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, chremophor, Miglyol 182 (commercially available from Dynamit Nobel Kay-Fries Chemical Company, Mont Vale, New Jersey), alcohol (e.g., ethanol, n-propyl alcohol or iso-propyl alcohol), liposomes or liposome-like products, silicone fluids and mixtures thereof.

Examples of artificial tear excipients which can be advantageously used in the practice of this

invention are isotonic sodium chloride, cellulose ethers such as hydroxypropylmethylcellulose and hydroxyethylcellulose, polyvinyl alcohol and other commercially available artificial tear solutions. An example of a useful polymeric excipient is polyoxyethylated castor oil. Examples of pharmaceutically acceptable membranes which can advantageously be used in the practice of this invention are: microdone, an artificial lipid membrane, polyvinylalcohol, or methylcellulose.

Cyclosporins which are useful in the practice of the present invention include both natural or synthetic cyclosporins. Cyclosporin A is preferred in the practice of the present invention. Other forms of cyclosporins (e.g., analogs and isomers such as Cyclosporins B, C, D, E, and H) may also be used. Mixtures of different cyclosporins may be used.

In the preferred method of treating a specific antigen mediated immune response in a patient having more than one involved site of the immune mediated response, the cyclosporin is applied locally to each involved site. For example, where only one eye appears to suffer from immune mediated KCS, both eyes should be treated. Surprisingly, unless each involved site is treated with cyclosporin, no appreciable benefit is obtained from cyclosporin treatment at any one of the sites, i.e., if only the affected eye is treated, little benefit of the cyclosporin is obtained. This suggests that locally administered cyclosporin interferes with and blocks the afferent immune recognition of the specific antigen which triggers the immune mediated response. Unless each of the sites wherein the specific antigen occurs is

treated with the cyclosporin, T-cell antigen signaling occurs continuously in the untreated site causing local lymphokine production that triggers a cascading systemic immune response that adversely affects both the treated and untreated sites.

In other words, local administration of cyclosporin acts to inhibit the continuous afferent immune response, for example within an eye, when antigens placed in the eye are associated with intraocular MHC antigen bearing accessory cells and are presented to T-cells. However, if an untreated eye or a distal skin graft is used to initiate antigen recognition, an afferent immune response begins at the site distal to the treatment site, T-cells are activated, lymphokines produced, and the systemic immune response proceeds to an efferent immune response affecting both eyes.

Thus, in any experiment in which an intrasubject control eye is used, local therapy in one eye will have diminished effect unless it is given in such quantity as to produce systemic immuno-suppression. Moreover, when treating an immune mediated response which exists to a much greater degree at one site of a patient, such as in or near one eye of the patient, than at another site of the patient, such as in the other eye of the patient, so as to be apparent at only the one site, the cyclosporin is advantageously administered locally in a therapeutically effective amount to each of the sites. An immune mediated response which appears to exist in only one eye of a patient is advantageously treated by administering a therapeutically effective amount of a cyclosporin

locally to both eyes of the patient to achieve maximal benefit.

If administered locally to each of the sites of the patient affected by the immune mediated response, cyclosporin can be used advantageously to treat a variety of immune mediated disorders. Ocular diseases which are successfully treated in animal models by local administration of cyclosporin to each site of the patient effected by the immune mediated response include immune-mediated melting ulcers in cats and dogs, chronic neovascularization and proliferative keratitis in cats and dogs, stromal keratitis subsequent to ulcerative Herpes keratitis in cats, pigmentary keratitis in dogs and KCS in dogs.

Numerous advantages accrue with the practice of the present invention. The method of the present invention is useful in that it can locally prevent activation of a pre-systemic response. Topical administration of a cyclosporin into a patient's tear deficient eye increases tear production in the eye. Thus, such treatment further serves to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea. Furthermore, cyclosporin directly decreases the immune response of granulation and neovascularization in the cornea.

Further objects of this invention, together with additional features contributing thereto and advantages accruing therefrom, will be apparent from the following examples of the invention.

Example 1: Effectiveness and distribution of topical cyclosporin.

Topical administration to a patient's eye has surprisingly been found to be an excellent method for providing a cyclosporin to the lacrimal glands of the patient to treat KCS. Additionally, since by its very nature topical administration does not require cyclosporin dispersion throughout the patient's system as is the case with systemic administration, the present invention provides a means for directing cyclosporin to the desired location without the accompanying high risk of adverse responses and high cost associated with systemic treatments.

Cyclosporin concentration has been determined for various eye compartments and tissues surrounding the eye after bilateral topical administration of cyclosporin to the eyes of three rabbits. The cyclosporin was administered in each of the rabbits' eyes in drops (approximately 17 microliters) of 2% radiolabelled cyclosporin in an olive oil solution applied every 15 minutes for 6 applications, followed by a period of two hours to allow for absorption. The rabbits were then euthanized and the eyes and surrounding tissue enucleated and frozen. The eyes and surrounding tissue were dissected into their component parts. These were then digested in collagenase and the resulting solutions analyzed by liquid scintillation counting for cyclosporin content. The following average cyclosporin concentrations were measured:

Accessory lacrimal gland: 2850 ng of cyclosporin/gram of tissue;

Periorbital fat: 800 ng/gram;

Cornea: 4700 ng/gram;

Iris: 1200 ng/gram;

Retina: 50 ng/gram;

Aqueous humor: 30 ng/gram;

Vitreous humor: 30 ng/gram;

Anterior sclera: 3150 ng/gram; and

Posterior sclera: 1550 ng/gram.

Example 2: Comparison of treatment of dry eye with anti-inflammatory steroid and cyclosporin.

A one year old standard female Poodle with conjunctivitis exhibited mild aqueous tear deficiency in both eyes. The dog had a Schirmer tear test value of 15 mm/minute in the right eye and 10 mm/minute in the left eye.

The Schirmer tear test is a test of aqueous tear production. The test depends upon observing the extent of wetting of a strip of filter paper placed over the lower lid of an eye for a specified time. Standardized strips are commercially available. The strip is folded at a notched marking and is then placed over the edge of the lateral one-third of the eyelid. The strip is usually left in place for a period of time while the patient looks straight ahead in dim light.

The degree of wetting of the paper is measured in mm from the notch. For human patients, a normal end point is 5 mm of wetting at five minutes. For canine patients, the normal tear production is 14 to 20 mm of wetting at one minute.

The dog was originally treated with dexamethasone by topical administration in both eyes four times daily. Although initially somewhat effective, treatment was subsequently discontinued and the same dog at approximately six years old still exhibited conjunctivitis in both eyes and had a Schirmer tear test value of 3 mm/minute in both eyes. Topical dexamethasone was then applied to both eyes twice daily for nine weeks without benefit.

The dog was then treated by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily without any other medications. After ten days, the dog showed markedly increased tear production and had a Schirmer tear test value of 22 mm/minute in the right eye and 8 mm/minute in the left eye.

The treatment by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily was continued for an additional three weeks. At this time, the dog exhibited plentiful aqueous tear production and the treatment was stopped for one week. After the one week, the dog had a Schirmer tear test value of 10 mm/minute in the right eye and 9 mm/minute in the left eye.

At this time, the treatment by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily was reinstituted and continued for six days. After the six days, the dog had a Schirmer tear test value of 22 mm/minute in the right eye and 16 mm/minute in the left eye.

In this case, a dog with chronic tear deficiency in which prior use of corticosteroids failed to improve tear secretion showed a surprising increase in

tear production with cyclosporin treatment. The increased tear production continued only while cyclosporin therapy continued. When the treatment was stopped for a week, the eyes again became tear deficient. However, tear production increased to normal levels after the treatment was restarted.

Example 3: Treatment of dry eye and enhancement of corneal healing with topical cyclosporin treatment.

An eight year old male Lhasa Apso had a four year old cat scratch in his left eye and an active 4 mm stromal ulcer in his right eye. An ocular examination of the dog showed conjunctivitis in both eyes with mucopurulent discharge, diffuse irregular corneal surfaces, pigment formation and neovascularization in the cornea of the left eye. The Schirmer tear test values were 12 mm/minute in the right eye and 3 mm/minute in the left eye.

The dog was treated with topical administration to both eyes of 2% cyclosporin in an olive oil solution once daily, neosporin twice daily and ophthalmic petrolatum. After five days, the Schirmer tear test values were 22 mm/minute in the right eye and 23 mm/minute in the left eye. In addition, the ulcer in the right eye was healed to 2 mm and the left eye was assessed to have decreased vascularization.

In this case, cyclosporin increased tear production significantly in a short period of time. Moreover, cyclosporin, unlike corticosteroids, did not retard corneal healing nor activate corneal collagenase. Accordingly, cyclosporin can be used in eyes having active corneal ulcers.

Example 4: Comparison of treatment of dry eye with pilocarpine alone and in combination with cyclosporin.

A six year old male English Bulldog with a long history of KCS had Schirmer tear test values of 2 mm/minute in the right eye and 3 mm/minute in the left eye.

The right eye was neovascularized over the entire cornea. No intraocular detail could be visualized through the opaque cornea. The cornea was grossly thick and irregular in surface. The left eye had neovascularization over about half of the cornea, mostly axially.

The dog was treated with three drops of 2% pilocarpine by mouth. After two hours, the Schirmer tear test values were 0 mm/minute in the right eye and 10 mm/minute in the left eye.

The dog was then treated with 2% cyclosporin in an olive oil solution administered topically to both eyes once daily and three drops of 2% pilocarpine administered by mouth twice daily. After twelve days, the Schirmer tear test values were 10 mm/minute in the right eye and 15 mm/minute in the left eye.

In this case, while pilocarpine alone increased tear production in the left eye from a Schirmer tear test value of 3 mm/minute to 10 mm/minute, pilocarpine did not increase tear production in the right eye. Use of cyclosporin with pilocarpine increased tear production to a Schirmer tear test value of 15 mm/minute in the left eye and from 0 mm/minute to 10 mm/minute in the right eye. The use of cyclosporin markedly increased tear production over the use of pilocarpine alone.

Example 5: Correction of dry eye and restoration of normal vision by topical treatment with cyclosporin.

A seven year old Miniature Poodle had a history of severe KCS of six to seven months duration. Treatment with artificial tears six times daily did not affect the apparent blindness.

The dog showed marked mucopurulent discharge in both eyes. The Schirmer tear test values were 0 mm/minute in both eyes. The dog's corneas were thickened and neovascularized with an irregular surface. No intraocular detail could be visualized through the opaque corneas.

The dog was treated with one drop of 2% pilocarpine by mouth two times daily and ophthalmic petrolatum four times daily. After two weeks, the Schirmer tear test values were still 0 mm/minute in both eyes. The corneal vascularity and scarring remained dense and the anterior chambers of the dog's eye were not visualizable.

The dog was then treated with 2% cyclosporin in an olive oil solution administered topically in both eyes once daily and two drops pilocarpine administered by mouth twice daily.

After two weeks, the Schirmer tear test values were 8 mm/minute in the right eye and 6 mm/minute in the left eye. Although corneal vascularization and scarring remained, the iris and lens could be evaluated, there was no mucoid discharge in either eye as previously and the KCS was assessed as medically improved.

After similar treatment for another two months, the Schirmer tear test values were 11 mm/minute in the

right eye and 17 mm/minute in the left eye. The dog's eyes had minimal corneal vascularization and minimal scarring.

In this case, although the dog was treated initially with pilocarpine, pilocarpine alone is not known to cause such a drastic improvement in tear production. After treatment with cyclosporin, the dog improved from no tear flow in either eye to normal tear production in both eyes. The dog improved from blinding corneal inflammation to very mild corneal pigmentation in both eyes. Treatment with cyclosporin markedly increased tear production and allowed the dog to return to normal vision.

Example 6: Stimulation of tearing in normal dogs.

Studies were conducted on the effect of applying topical 2% cyclosporin in olive oil to the eyes of normal dogs. The results are shown in Figure 1 comparing the effect of topical cyclosporin on lacrimination in six normal male beagle dogs, before and after several days of olive oil therapy alone. In both studies, no treatment was given on days 1 to 3 to establish a baseline. On days 4-10, as graphed by the triangles, one drop of olive oil was administered twice daily (BID) to each eye. On days 11-13, one drop of 2% cyclosporin in olive oil was administered twice daily. A significant increase in tearing was observed. On days 4-10, as graphed by the squares, one drop of 2% cyclosporin in olive oil was administered twice daily. On days 11-13, one drop of olive oil was applied to each eye twice daily. The significant increase in tearing observed over days 4-10 persisted through days 11-13 in the absence of cyclosporin treatment.

The data conclusively demonstrate that topically applied cyclosporin increases glandular function, i.e., lacrimination, in normal eyes.

Since cyclosporin has very low solubility in most solutions which can be administered to the eye, the cyclosporin in the majority of studies on the efficacy of topical administration of cyclosporin has been suspended in olive oil. Unfortunately, controlled studies comparing olive oil alone and in combination with cyclosporin demonstrate that the vehicle, the olive oil, produces redness and burning. In animals, pain is evidenced by the animal holding its eyes shut. In approximately 5 to 10% of approximately 1000 months of treatment (based on number of bottles of 2% cyclosporin dispensed for veterinary use where one bottle is sufficient for treatment of an animal twice daily for about one month), other side effects were observed, including lid edema, corneal surface irregularities, and periocular alopecia.

The present invention includes the surprising discovery that corn oil can be substituted for olive oil as the vehicle for topical administration of cyclosporin to the eye to avoid the undesirable side effects due to the use of the olive oil. Over 3000 bottles of 2% cyclosporin have now been dispensed for treatment of animals twice daily without any apparent side effects for periods of time up to four months.

Additives to the corn oil which enhance stability of the cyclosporin solution include antioxidants such as alpha tocopherol and preservatives such as methyl paraben. Other antioxidants are known to those skilled in the art.

There are some indications that alpha tocopherol (Vitamin E) may also have beneficial effects on the eye since oxidative radicals increase inflammatory damage. Preliminary clinical observations on the protective action of oral administration of vitamins A and E on the corneal epithelium were recently published by Gerhardinger, et al., in Acta Vitaminol. Enzymol. 7(Supp),71-74 (1985). Other compounds which may be added to the cyclosporin solution include emollients, viscosity modifying agents, antioxidants, preservatives, antibiotics, antifungals, antivirals, lubricants, surfactants, vasoconstrictors, DMSO, parasympathomimetics, cholinergics, neurotransmitters, lacrimogenic agents, substance P agonists, substance P antagonists, mucolytics, prostaglandin antagonists, lipogenase inhibitors, cyclooxygenase inhibitors, antiinflammatories, oxygen scavengers, hydrating agents, and epitheliotropic agents. Specific examples, in addition to alpha tocopherol and methyl paraben, include vitamin A, retinoic acid, pilocarpine, hyaluronic acid, polyvinyl alcohol, methylcellulose, eledoisin, physalaemin, bromhexine, mucosolvan, acetylcysteine, indomethacin, and corticosteroids.

The most preferred formulation at this time for topical ophthalmic use consists of 2% cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben. However, cyclosporin solutions can be prepared of between approximately 0.01% by weight and saturation, approximately 20% by weight. Unless otherwise specified, all percentages of compounds herein are by weight.

Although the usual means of administration of the compound is by administration of cyclosporin drops to the surface of the eye, delayed or prolonged release of the cyclosporin at a selected site can also be achieved by encapsulating the cyclosporin-oil mixture within a polymeric implant, liposomes, or microcapsules. Methods for making polymeric implants for ocular use are taught by U.S. Patent No. 3,960,150 to Hussain et al. Both non-degradable and biodegradable polymers can be used, including polyethylene, polystyrene, polypropylene, polyanhydrides, polyorthoester, polylactic acid, and polyglycolic acid. Methods for encapsulating materials within liposomes are taught by PCT/US85/00220 publication WO 85/03640 29 August 1985 by the Liposome Company. Methods for encapsulation of biological material within microcapsules for implantation are taught by U.S. Patent No. 4,352,883 to Lim. Other suitable methods and materials are known to those skilled in the art.

The following non-limiting examples demonstrate the efficacy and advantages of topical cyclosporin in corn oil for treatment of immune disorders, enhancement or restoration of tear production, and enhancement or effecting of normal healing of the surface of the eye.

Example 6: Stimulation of tearing in normal dogs.

Studies were conducted on the effect of applying topical 2% cyclosporin in olive oil to the eyes of normal dogs. The results are shown in Figure 1 comparing the effect of topical cyclosporin on lacrimination in six normal male beagle dogs, before and after several days of olive oil therapy alone. In

both studies, no treatment was given on days 1 to 3 to establish a baseline. On days 4-10, as graphed by the triangles, one drop of olive oil was administered twice daily (BID) to each eye. On days 11-13, one drop of 2% cyclosporin in olive oil was administered twice daily. A significant increase in tearing was observed. On days 4-10, as graphed by the squares, one drop of 2% cyclosporin in olive oil was administered twice daily. On days 11-13, one drop of olive oil was applied to each eye twice daily. The significant increase in tearing observed over days 4-10 persisted through days 11-13 in the absence of cyclosporin treatment.

The data conclusively demonstrate that topically applied cyclosporin increases glandular function, i.e., lacrimination, in normal eyes.

Example 7: Topically applied cyclosporin: Lacrimomimetic effects and reduction of corneal scars in dogs with KCS.

Twenty five cases (22 bilateral, 2 unilateral cases) of spontaneous KCS were treated with a solution of 2% cyclosporin (CsA) in olive oil, 1 gtt QD - BID, OU, and evaluated for changes in tear production as determined by Schirmer tear test (STT) and for changes in the surface of the globe.

The effects of cyclosporin were twofold: cyclosporin increased tear production in 84% of idiopathic cases of canine KCS and cyclosporin caused marked regression of corneal pathology including superficial granulation tissue, neovascularization and pigmentation, without retarding healing of corneal ulcers. Case histories are summarized in Table 1.

The diagnosis of KCS preceded CsA use by 0-60 months, with an average of 1.1 yr. Prior treatment included artificial tears in 16/25 dogs, oral or topical pilocarpine in 11/25 dogs, oral or topical corticosteroids in 11/25 dogs, topical antibiotics in 9/25 dogs, or no prior treatment in 5/25 dogs.

Contrary to expectation, the longevity of KCS did not correlate inversely with response to therapy. The average STT before administration of cyclosporin was 2.54 mm/min right eye and 2.46 mm/min left eye. During the period in which cyclosporin eyedrops were administered, the mean STT value was 11.38 mm/min right eye and 11.50 mm/min left eye. The average increase in STT was 8.84 mm/min right eye ($t = 7.5$ Student's T -test for related measures, $p<0.0005$), and 9.04 mm/min left eye ($t = 6.7$, $p<0.0005$). 38 eyes were initially diagnosed as having severe KCS (STT 0-4 mm/min). Following treatment, STT values increased by greater than 5 mm/min in 84% of severely affected eyes. Dogs were noted to have increased STT beginning 3 to 56 days after onset of cyclosporin therapy. Of the six eyes (6/38, 16%) determined to be nonresponsive, five were evaluated for only a short period (7 to 35 days). Because STT value in responsive eyes increased with increased frequency and duration of treatment (see Table I, cases 21 and 22), the 84% success rate may be an underestimate.

In six dogs whose STT values increased in response to cyclosporin, treatment was discontinued and the STT values regressed. When cyclosporin was reinstituted, the STT increased back to maximal levels in six hours in one case, and in 1-7 days in the other four cases. In two dogs receiving cyclosporin on

alternate days, the STT values decreased on nontreatment days. Even with sporadic interruptions in administration of cyclosporin treatment, no dog has lost responsiveness to cyclosporin. Many of the cyclosporin responsive dogs previously had been unresponsive to corticosteroids administered topically, subconjunctivally, and parenterally.

In dogs with superficial corneal granulation tissue, continuous use of cyclosporin resulted in a progressive decrease in the abnormal thickness and opacity of the cornea. Even in dogs that did not have an increase in tear secretion, alleviation of the corneal disease was generally marked. Most dogs with dense blinding pigmentation and superficial granulation had marked clearing of the corneas after several months of treatment. Three dogs had corneal ulcers at the onset of treatment with cyclosporin; each healed within 48 hours of onset of treatment. Dogs maintained for prolonged periods (8-12 months) relapsed into KCS within 2-3 days of withdrawal of cyclosporin.

TABLE 1. Previous ocular therapy, and Schirmer tear test (STT) values before and while using, cyclosporin eyedrops in 25 cases of canine keratoconjunctivitis sicca.

Case #, Breed, Sex, Age +/-Keratitis (response to CsA)	Treatment Interval/ Frequency	STT Values Before CsA OD/OS	STT Values With CsA OO/OS
1. Standard Poodle, F,7 yr no keratitis	6 wk/QD	3/3	22/16
2. Cocker Spaniel, F 7 yr, Pigmentary keratitis (marked improvement)	5 mo/BID	0/0	10/13
3. Min. Schnauzer, F/S, 11 yr, Pigmentary keratitis (Marked improvement)	5 wk/QD	2/0	8/1
4. Eng. Bulldog, M, 7yr, Chronic keratitis, visual deficits (Resolved)	7 wk/BID	2/3	13/20
5. Samoyed, F/S, 14 yr, mild keratitis (Resolved)	1 mo/BID	2/11	18/17
6. Shih-tzu, M, 10 yr Pigmentary keratitis, visual deficits (Marked improvement)	13 wk/QD	4/10	13/14
7. Min. Poodle, M, 7 yr, blind dt corneal scarring (Resolved completely)	16 wk/BID	0/0	11/17
8. Mixed breed, F/S, 5 yrs diffuse fluorescein uptake (No staining)	8 mo/BID	0/0	19/17
9. W H W Terrier, F/S 5 yr, Pigmentary keratitis/blind (Improved visual)	4 wks/QD	0/0	13/0
10. Shih tzu M 4 yr, Chronic keratitis OD (Much improved)	26 wk/QD	15/1	15/6

Table 1 continued (page 2)

11. Poodle x, F, 6 yr, Mild superficial keratitis (Improved)	22 wk/QD	0/0	12/18
12. Shih tzu, F, 3 yr, Pigmentary keratitis (Marked Improvement)	17 wk/QD	0/0	3/10
13. Dachshund F, 10 yr, Minimal superficial keratitis (Resolved)	15 wk/BID	5/0	10/2
14. Scottish Terrier, M, 12 yr, Pigmentary keratitis (50% resolution)	9 wk/QD	6/8	12/18
15. Lhasa Apso M/C, 10 yr Pigmentary keratitis (50% resolution)	8 wk/QD	13/1	18/19
16. Lhasa Apso M, 9 yr, Pigmentary keratitis (Slight Improvement)	5 wk/QD	8/16	19/22
17. Min. Schnauzer, M, 11 yr Pigmentary keratitis/ blind (Slight improvement)	9 wk/BID	0/4	5/10
18. Min. Poodle F, 7 yr Marked keratitis (Marked improvement)	5 wk/QD	0/0	2/1
19. Cocker Spaniel, F, yr 1.5 yr, no keratitis	5 wk/QD	7/5	15/10
20. Boston terrier, F/S, 7 yr, no keratitis	6 wk/QD	4/4	14/19
21. Dachshund, M, 3 yr, Mild superficial keratitis (Nearly resolved)	4 wk/BID	1/5	3/17

Table 1 continued (page 3)

22. Peke/Pomeranian X, F/S 5 yr,Pigmentary keratitis 100% (50% improved)	12 wk/BID	0/0	20/18
23. Min. Poodle, M, 9 mo. Chronic keratitis (Marked improvement)	4 wk/QD	4/4	13/13
24. Toy Poodle, F/S, 15 yr Chronic keratitis, visual loss (Marked improvement)	7 wk/BID	3/0	16/0
25. Peke/Pomeranian, F/S, 6 yr, Pigmentary keratitis, blind (Marked improvement/ visual)	11 wk/BID	0/0	8/8

Abbreviations: F (female), M (male), C (castrated), S (spayed), CsA (2% cyclosporin), QD (once daily), BID (twice daily)

Corneal lesions and changes in the corneal lesions were bilateral unless otherwise indicated.

Example 8: Stimulation of tearing in humans suffering from Sjogren's syndrome.

Sjogren's syndrome is characterized by chronic infiltration of the exocrine glands, principally the lacrimal and salivary glands, by mononuclear leukocytes. The process causes the progressive destruction of the glandular tissue and is characterized by the development of keratoconjunctivitis sicca (KCS), or "dry eye". Neither topical nor parenteral treatment using steroids has been completely effective in decreasing irritation of the corneal surface nor in preventing corneal ulcer formation. In fact, topical or parenteral corticosteroids do not enhance lacrimation and can retard healing of corneal ulcers and are therefore considered to be contraindicated by many ophthalmologists.

A human patient with primary Sjogren's syndrome (dry eye with dry mouth) was treated with topical 2% cyclosporin in corn oil. The patient had been treated for years with conventional therapy, artificial tears Q 15 mins. For the past several months his STT were 2-3 mm/5min/eye. (In humans the STT is measured for 5 minutes, unlike the dog where it is measured for only 1 min. However, the expected normal values are the same, i.e., normal is 14 mm, values under 5 mm are indicative of a severe case of dry eye).

Following 9 days of twice daily therapy of both eyes, his STT was 20 and 23 mm/5 min/eye, a significant increase over the pretreatment values. Prior to treatment, the corneas had stained diffusely in both eyes with fluorescein dye, an indication of corneal ulcers. After 9 days of therapy, one eye had

no staining and one eye only stained over 1/3 of the surface.

Three women with severe chronic secondary Sjogren's syndrome were treated for 1 week with BID 2% cyclosporin in corn oil containing 1 mole% alpha tocopherol and 0.005%methyl paraben. All three had abnormal corneas. The first had a nonhealing corneal ulcer which penetrated the full thickness of the surface epithelium covering the cornea. This ulcer healed within two days of onset of therapy. The second had a "contact lens cornea", an indentation at the circumference of the cornea which gives it the appearance of an eye wearing a contact lens, when no lens is present, which is analogous to a scar. The indentation showed evidence of filling in within 7 days of therapy. The third had corneal lesions which also showed improvement within one week. All had increases in the STT.

The results conclusively demonstrate the effectiveness of topically administered cyclosporin in alleviating the symptoms of KCS, promoting normal healing and actually reducing scar tissue on the surface of the eye.

Example 9: Promotion of normal healing of the eye surface without restoration of normal tearing in a dog.

An 11-year old spayed Miniature Schnauzer had been determined to have KCS 8 months before admission. Analysis of a specimen obtained by conjunctival scraping at that time revealed distemper virus. The dog had been treated with 2% pilocarpine, (1 gtt PO q 12 h) which initially caused an increase in the STT to 8 mm/min bilaterally but later lost efficacy, as

the STT decreased to 0 mm/min bilaterally. Treatment had been dexamethasone ointment Q 12 h bilaterally, artificial tears approximately 6 times daily, and petrolatum ointment at bedtime. On admission, ophthalmic observation showed the STT to be 2 mm/min right eye, 0 mm/min left eye, with mucoid conjunctivitis bilaterally, dorsal corneal pigmentation of approximately 40-50% of the corneal surface, and superficial neovascularization extending approximately 6 mm into the dorsal half of the cornea bilaterally (Fig. 2B). The corneal surfaces were modeled irregularly but translucent, and there were no apparent visual deficits. Complete blood count and serum thyroxin were normal and the only abnormality detected on serum profile was an elevated serum alkaline phosphatase (667 mg/dl).

Cyclosporin (2% 1 gtt QD, bilaterally) was prescribed, with artificial tears to be administered as needed. In 4 weeks, the STT had increased to 8 mm/min in the right eye but was still 0-1 mm/min in the left eye. The conjunctivitis had improved, but was still evident in the left eye. However, there was marked improvement of the corneal surface bilaterally (Fig. 2B).

A parotid duct transposition was performed at this time and the lacrimal gland of each third eyelid biopsied. Microscopically both glands were similar, with diffuse often intense periductal and interstitial infiltration of plasma cells and lymphocytes, and fibrosis of the acini and tubules. Focal areas of normal acinar tissue were seen in each gland, and some areas contained dilated tubules lined with flattened epithelium. The results in the preceding examples

establish that topically applied cyclosporin can be used to resolve corneal ulcers even in the absence of restoration of tearing. As dramatically shown by Figure 2A and 2B, the eye surface becomes clearer, smoother, and vision is improved.

Example 10: Comparison of olive oil and corn oil vehicles for cyclosporin for topical ophthalmic use.

Among the animals treated with cyclosporin in olive oil, within four days of beginning treatment, four dogs and one cat had ocular irritation reactions including: hyperemia of the bulbar conjunctiva, corneal surface irregularities with apparent corneal edema, and blepharospasms indicative of ocular pain.

In each case therapy was withdrawn and these symptoms resolved. Therapy with cyclosporin in corn oil was begun in three of the dogs following resolution of the ocular irritation reactions. All three dogs tolerated the corn oil/cyclosporin mixture well.

In the fourth dog, cyclosporin in olive oil was used less frequently than the BID prescription because the owner thought the drug irritated the eyes, but kept using it on an infrequent basis. Following two to three weeks of use, bilateral periocular alopecia occurred and the lids were intensely hyperemic. The cyclosporin in olive oil was discontinued for several weeks. Cyclosporin in corn oil was begun BID bilaterally. The lesions of chronic corneal vascularization and superficial keratitis resolved markedly, the STT increased, and there was no recurrence or irritation or alopecia.

Olive oil and corn oil were also compared in normal, human eyes. The olive oil produced a burning sensation lasting 15 to 60 minutes. The corn oil produced a milder sensation lasting only 1 to 2 minutes.

No side effects have been noted in the any of the 3000 bottles of 2% cyclosporin in corn oil dispensed for animal use, in comparison with the 5 to 10% incidence of side effects in 1000 bottles of 2% cyclosporin in olive oil dispensed for animal use. The substantial difference in tolerance of the two oils is surprising since the chemical nature of olive oil and corn oil is very similar. Tests of the levels of free fatty acids and pH do not indicate any significant differences which could account for the decreased tolerance for olive oil. Substitution of purified olive oil, Sigma Chemical Co., St. Louis, MO, or first press olive oil, for the Berio brand olive oil, obtained from the grocery store, which was used initially, does not eliminate the irritation.

Modifications and variations of the present invention, an improved cyclosporin composition for topical ophthalmic use, will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

CLAIMS:

1. A method of enhancing or restoring lacrimal gland function comprising topically administering a cyclosporin.

2. The method of claim 1 for increasing tear production in a tear-deficient eye comprising topically administering a therapeutically effective amount of a cyclosporin to the eye.

3. The method of claim 1 wherein said cyclosporin is administered as a solution, suspension or ointment comprising between approximately 0.01 to 50 weight percent of cyclosporin in a pharmaceutically acceptable excipient.

4. The method of claim 3 wherein said cyclosporin is administered in an amount of 0.1 to 20 weight percent.

5. The method of claim 3 wherein the pharmaceutically acceptable excipient comprises corn oil, olive oil, arachis oil, castor oil, polyoxyethylated castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, an alcohol, liposome, silicone fluid or a mixture thereof.

6. The method of claim 1 wherein said cyclosporin is Cyclosporin A.

7. The method of claim 1 for increasing tear production in an eye of a patient suffering from an autoimmune dysfunction of the lacrimal glands comprising administering a therapeutically effective amount of a cyclosporin topically to the patient's eye.

8. The method of claim 1 for treating keratoconjunctivitis sicca in a patient comprising the step of administering a therapeutically effective amount of a cyclosporin topically to both of the patient's eyes.

9. The method of claim 1 for treating a disorder caused by excessive immune activity in a lacrimal gland of a patient comprising the step of topically administering to both of the patient's eyes an amount of a cyclosporin sufficient to reduce the immune activity.

10. The method of claim 1 for treating a disorder exacerbated by kerato-conjunctivitis sicca in a patient comprising administering to the patient's eye a therapeutically effective amount of a cyclosporin to promote corneal healing.

11. A topical ophthalmic composition comprising

cyclosporin in a corn oil base.

12. The composition of claim 11 wherein the concentration of cyclosporin is between about 0.01% and saturation.

13. The composition of claim 11 further comprising a compound selected from the group consisting of emollients, viscosity modifying agents, antioxidants, preservatives, antibiotics, antifungals, antivirals, lubricants, surfactants, vasoconstrictors, DMSO, parasympathomimetics, cholinergics, neurotransmitters, lacrimogenic agents, substance P agonists, substance P antagonists, mucolytics, prostaglandin antagonists, lipogenase inhibitors, cyclooxygenase inhibitors, antiinflammatories, oxygen scavengers, hydrating agents, and epitheliotropic agents.

14. The composition of claim 13 wherein the compound is selected from the group consisting of vitamin A, vitamin E, retinoic acid, pilocarpine, hyaluronic acid, polyvinyl alcohol, methylcellulose, methyl paraben, eledoisin, physalaemin, bromhexine, mucosolvan, acetylcysteine, indomethacin, and corticosteroids.

15. The composition of claim 11 comprising 2% cyclosporin in corn oil.

16. The composition of claim 15 further comprising a compound selected from the group consisting of alpha tocopherol and methyl paraben.

17. The composition of claim 11 wherein said composition is encapsulated.

18. The composition of claim 17 wherein said composition is encapsulated within a polymeric matrix.

19. The composition of claim 18 wherein said composition is encapsulated within a polymeric matrix formed of a polymer selected from the group consisting of polyethylene, polystyrene, polypropylene, polyanhydrides, polyorthoester, polylactic acid, and polyglycolic acid.

20. The composition of claim 17 wherein said composition is encapsulated within liposomes.

21. The composition of claim 17 wherein said composition is microencapsulated.

22. The composition of claim 11 wherein said cyclosporin is in a concentration which promotes normal wound healing.

23. The composition of claim 23 wherein said cyclosporin is in a concentration which stimulates or restores lacrimal gland activity.

24. The composition of claim 11 wherein said cyclosporin is in a concentration which suppresses an immune disorder.

FIG.I
Topical Cyclosporine 2%: Effects on Lacrimation

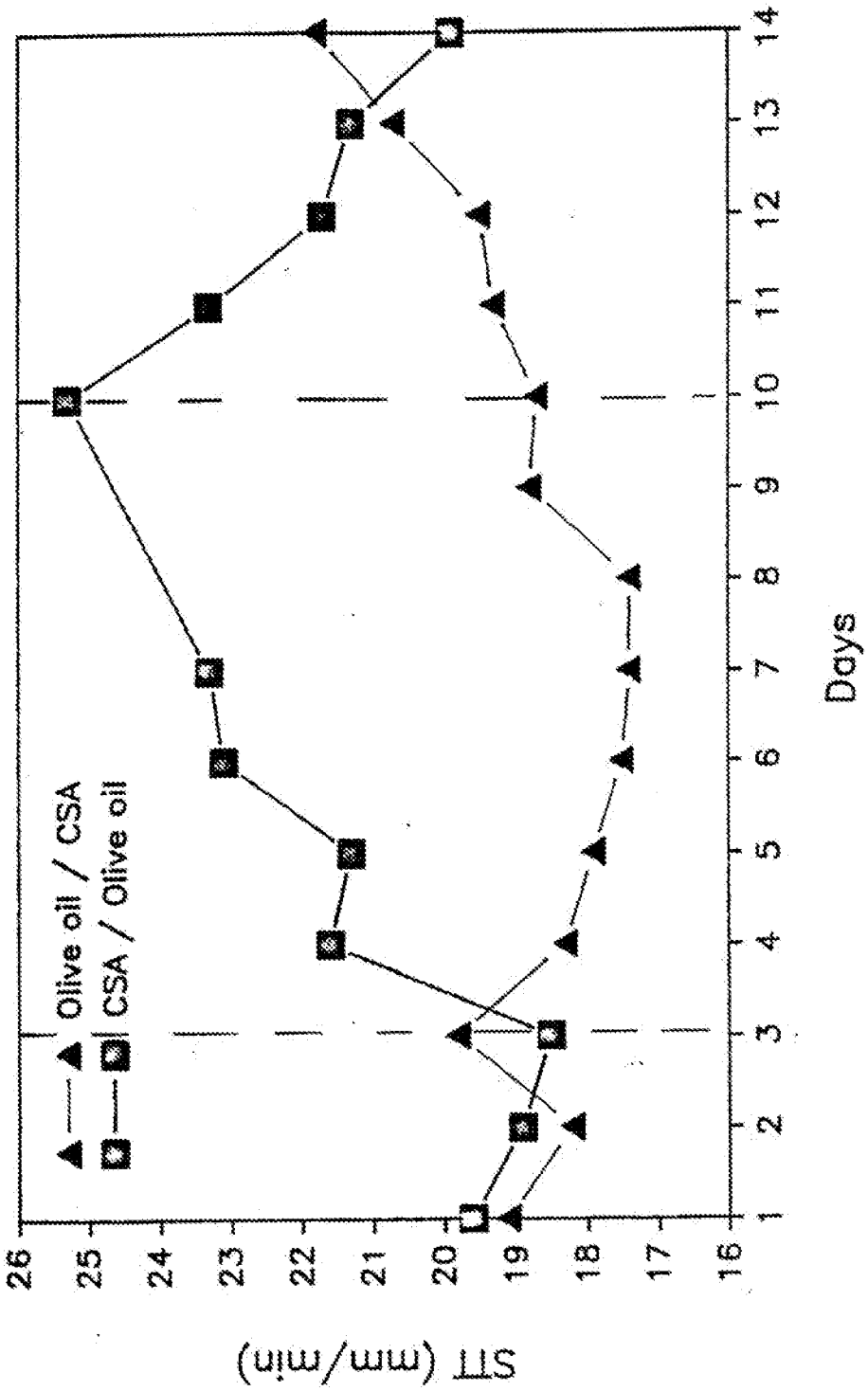


FIG. 2A

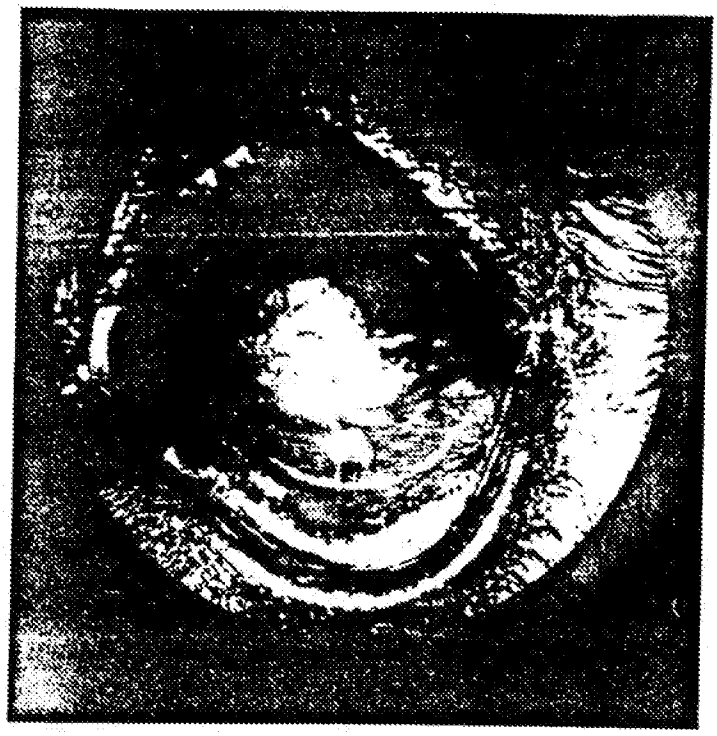
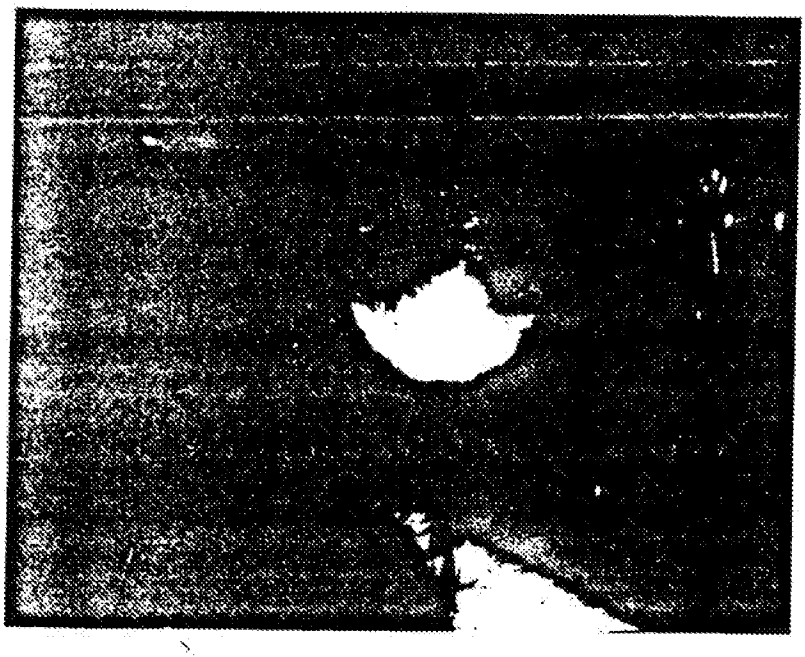


FIG. 2B



INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/03039

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/00; A 61 K 9/08; A 61 K 37/02

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4 649 047 (R KASWAN) 10 March 1987 see claims 5-11, column 3 and 6 --	11,12,15,24
Y	Dialog Information Services, File 351: WPI 81-88, 51 accession no 4331684 (WPI accession no. 86-335072), H. Mizushima: "Eyedrops composed of lipid microspheres contg. remedies for eye troubles", & JP, A, 61249918, published 7 November 1986 --	11,15,17,20, 21
Y	US, A, 3 608 073 (R E PHARES JR) 21 September 1971 see claim 1, example 4 --	11,15
Y	KLIN MBL AUGENHEILK., Vol. 187, 1985, F. Hoffman et al.: "Lokale Behandlung des Hornhauttransplantates beim Menschen mit Cyclosporin A", pages 92-96, see page 95 --	11,12,14,15, 22,24

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th November 1988	28 DEC 1988
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 4 388 307 (T CAVANAK) 14 June 1984 see column 5, claims 9 and 15 --	11,12,24
Y	WO, A, 85/03640 (THE LIPOSOME COMPANY, INC) 29 August 1985 see page 14, line 32, claims 49 and 76 --	11,17,21
Y	US, A, 4 115 544 (J W SHELL) 19 September 1978 see claims --	11,13,14, 17-19,21
Y	EP, A, 0 224 352 (IMPERIAL CHEMICAL INDUSTRIES PLC) 3 June 1987 see claims 4, 6 and 8 --	11,13,14, 24
Y	DE, A, 3 526 545 (SANDOZ-PATENT-GMBH) 13 February 1986 see pages 4-5 ---	11,22-24

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-10 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy (Rule 39.1.iv)

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

PCT/US88/03039
SA 24168

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/11/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4649047	10-03-87	None	
US-A- 3608073	11-05-71	None	
US-A- 4388307	14-06-83	BE-A- 874628	05-09-79
		GB-A- 2015339	12-09-79
		NL-A- 7901703	11-09-79
		FR-A- 2419072	05-10-79
		DE-A- 2907460	13-09-79
		JP-A-54132223	15-10-79
		CA-A- 1139667	18-01-83
		CH-A- 636013	13-05-83
		AU-A- 528714	12-05-83
		SE-A- 7901683	08-09-79
		AT-A- 375828	10-09-84
		SE-A- 445174	09-06-86
WO-A- 8503640	29-08-85	EP-A- 0172907	05-03-86
		JP-T-61501686	14-08-86
		US-A- 4708861	24-11-87
US-A- 4115544	19-09-78	None	
EP-A- 0224352	03-06-87	JP-A-62142110	25-06-87
DE-A- 3526545	13-02-86	EP-A- 0170623	05-02-86
		JP-A-61043120	01-03-86

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 9/127, A61F 13/02

A1

(11) International Publication Number: WO 93/18752

(43) International Publication Date: 30 September 1993 (30.09.93)

(21) International Application Number: PCT/US93/02800

(22) International Filing Date: 25 March 1993 (25.03.93)

(30) Priority data:

101387	26 March 1992 (26.03.92)	IL
Not furnished	23 March 1993 (23.03.93)	US

(71) Applicant: PHARMOS CORP. [US/US]; 599 Lexington Avenue, New York, NY 10022 (US).

(72) Inventors: FRIEDMAN, Doron ; 33 Alon Street, 72 910 Karmei-Yosef (IL). SCHWARTZ, Joseph ; 40 Benjamin Street, Rehovot (IL). AVIV, Haim ; 9 Habrosh Street, Rehovot (IL).

(74) Agents: WEILD, David, III et al.; Penny & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TOPICAL AND TRANSDERMAL DELIVERY SYSTEM UTILIZING SUBMICRON OIL SPHERES

(57) Abstract

The present invention relates to a delivery system which includes a bioactive drug or cosmetic substance presented in the form of submicron oil spheres alone, or drugs or cosmetic substances in a combination with the oil spheres in an aqueous suspension or emulsion. Optionally, a skin penetration enhancer may be included in such formulations. Such preparations achieve improved bioavailability and exert larger pharmacological effects than an equivalent dose of the drug or cosmetic formulated in conventional creams, lotions or oleaginous bases.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

TOPICAL AND TRANSDERMAL DELIVERY SYSTEM UTILIZING SUBMICRON OIL SPHERES

FIELD OF THE INVENTION

The present invention relates to the field of drug delivery and, particularly, to the administration of various pharmaceutical or cosmetic agents to a patient through the skin or mucous membranes by the application of innovative, non-irritating topical compositions of these agents in the form of submicron oil spheres.

BACKGROUND OF THE PRESENT INVENTION

The delivery of drugs to the skin and systemically via the skin is hampered by the natural barrier of the stratum corneum. Creams and lotions are classical vehicles for delivering drugs and cosmetics to the skin. These preparations are semi-solid, bi-phasic preparations where oil spheres are dispersed in water. The droplet size of these spheres has not been a concern in conventional pharmaceutically marketed semi-solid creams and lotions. Most commercially marketed medical creams include oil spheres having a size of 5 to 50 microns. For example, VOLTAREN EMULGEL has a droplet size above five microns, as confirmed both microscopically and with photon correlation spectroscopy (Coulter N4MD).

Moreover, the scientific literature does not address the droplet size of the internal oily phase of topically applied emulsions. On the few occasions that refer to topical cream or lotion dosage forms, the indicated droplet size is in the range of a few to tens of microns. For example, U.S. Patent 4,529,601 relates to an eutectic mixture of lidocaine and tetracaine which allegedly produces a good local anesthetic effect that may not be achieved otherwise.

EP 00 63 870 claims good anti-inflammatory activity and high safety of an anti-inflammatory substance in

combination with MCT oil and carboxy vinyl polymer. Again, droplet size is not emphasized.

EP 04 33 132 discloses the topical cosmetic application of vesicles for incorporation of essential oils. It is also possible, according to that patent application, that small droplets of various sizes of the essential oils may be formed.

The cases cited above exemplify numerous patents concerning topical uses of classical macroemulsions, in which the oily droplets are generally well above one micron in diameter. There is also a vast body of prior art utilizing liposome preparations for enhanced dermal penetration of pharmaceuticals (Egbaria & Weiner, Adv. Drug Delivery Rev. 5, 287 (1990)). However, there are inherent problems in formulating stable liposomes, since these structures are lipid bilayers enveloping an aqueous phase. Another type of drug carrier, distinct from both classical emulsions and liposomes are the microemulsions which are usually thermodynamically stable, transparent and have particles consistently below 200 nm (Rosano, H.L., Carallo, J.L. and Lyons, G.B. Microemulsion Systems, Vol. 24, Chap. 16, H.L. Rosano and M. Clause eds. Marcel Dekker, Inc., N.Y. (1987), pp. 271). However, microemulsions contain a large proportion of surfactant to lipid and therefore are inappropriate for dermal applications due to anticipated problems of irritancy.

EP 05 06 197 discloses an aqueous suspension of nanoparticles of at least one lipid and an emulsifier, wherein the nanoparticles have a size of between 50 and 1000 nm. The lipids used therein, however, are either a solid lipid or a mixture of solid lipids.

In the field of topical and transdermal medication and delivery of drugs, much effort has been invested in providing chemical enhancers of drug penetration, such as DMSO and azones. Many of these substances cause irritation and are not desirable due to their toxicity. There remains a need, therefore, for a method and vehicle

which will enable or facilitate efficient transport of poorly soluble drugs through the skin for topical or transdermal use, when provided as an aqueous dispersion of same.

SUMMARY OF THE INVENTION

This invention relates to a composition for topical application of pharmaceuticals or cosmetics comprising submicron size droplets of a drug with oily excipients either alone or dispersed in an aqueous medium. The droplet size is below one micron, and preferably in the range of about 0.05 to 0.5 microns. A semi-solid state is advantageous for the practical application of the dosage form on the skin when used as a cream.

Specifically, the submicron size droplets include about 0.5 to 30% of a first component comprising an oily liquid, about 0.1 to 10% of a second component of an emulsifier and about 0.05 to 5% of a non-ionic surfactant. These droplets are suspended in an aqueous component which forms the continuous phase of an emulsion. The composition provides enhanced topical and/or transdermal systemic effects compared to similar compositions which have larger size droplets. A mean droplet size in the range of between about 0.1 and 0.3 μm is preferred.

The first component is typically present in an amount of about 5 to 20%, and includes oily liquids such as a medium chain triglyceride oil having a chain length of about 8 to 12 carbons, a vegetable oil, a mineral oil, an oil of animal source, a synthetic derivative thereof, or mixtures thereof. To form a viscous composition, the oily liquid may be present in an amount of about 20 to 30%. Alternatively, one or more adjuvants such as gelling agents or thickening agents may be included to increase the viscosity of the composition and form a cream.

The emulsifier may be a phospholipid compound or a mixture of phospholipids, such as lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures

thereof, in an amount of about 0.2 to 5%. The surfactant may be a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups, such as an ethoxylated alcohol or ester compound, in an amount of about 0.2 to 5%.

The first component may comprise an active ingredient in any one of a number of forms. For simplicity, the active ingredient may be in the form of an essentially water-insoluble oily liquid, such that other oily liquids are either not needed or can be mixed therewith. Instead, the active ingredient can be present as a solid, essentially water-insoluble or slightly water-soluble substance which is partially or fully dissolved or dispersed in one of the oily liquids mentioned above. For such mixtures or dispersions, the active ingredient may be present in an amount of 0.05 to 2.5%.

The active ingredient may be one or more of the following: a steroid, non-steroidal anti-inflammatory drug, antibiotic, tranquilizer, sedative, anti-histaminic, antifungal, antibacterial, antiviral, disinfectant, antipsoriasis agent or a local anesthetic. Specifically, the active ingredient is clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin B, gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

The composition may also include a dispersion enhancer in an amount sufficient to promote the homogeneity of the composition, or a viscosity enhancing agent in an amount sufficient to impart a semi-solid form to the composition. A preferred viscosity enhancing agent is a physiologically acceptable high molecular weight compound. In addition, a skin penetration enhancer may be added in an amount sufficient to enhance the penetration of the composition through skin after the composition is topically applied thereto.

The invention also relates to a method for obtaining enhanced topical and/or transdermal systemic effects which

comprises formulating one of the compositions described above and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets. In this method, the active ingredient may be a barbiturate, benzodiazepine, ketotifen, phenytoin, phenothiazines, cyclosporin, diphenoxylate, diclofenac, dexamethasone, prostaglandin, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, lipophilic peptide or miconazole.

When the method is used to treat a skin condition, the active ingredient may be Vitamin A, Vitamin E, a retinoid, a carotene or benzoyl peroxide, and is applied to alleviate, reduce or prevent dermatological conditions and diseases, including atopic dermatitis, psoriasis, acne and other types of skin inflammations or viral, fungal or bacterial skin infections.

The invention also relates to a method for reducing local irritation produced by pharmaceuticals which induce local inflammatory reactions by topically applying one of the compositions described above. Depending upon the selection of the active ingredient, the method may be used for achieving local anesthesia or analgesia, or for providing general analgesia.

Also, an article, such as an occlusive dressing or adhesive patch, can be used to administer active ingredients such as a steroid, nicotine, nitroglycerine or the like.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following detailed description, reference will be made to the annexed drawings, in which:

Fig. 1 is a graphical illustration of the effects of edema over time during treatment with various diclofenac creams;

Fig. 2 is a graphical illustration of the relative difference over time during treatment with various diclofenac creams; and

Fig. 3 is a graphical illustration of the effects of edema over time during treatment with various naproxen creams.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, pharmaceutical and cosmetic compositions are provided in the form of submicron droplets of water-insoluble liquid drugs or cosmetically active substances alone, or drugs or cosmetically active substances with oily excipients and/or solvents in an aqueous medium. These compositions promote percutaneous penetration on topical application and local or transdermal effects. Advantageously, a chemical entity which acts as a skin penetration enhancer may be added to the above for enhancing activity. Thus, the overall pharmacological effect, while using such a chemical enhancer in conjunction with such submicron oil spheres, will be greater than either one of them alone.

In contrast to the prior art, the present invention relates to oily spheres having an average diameter in the submicron range, which are both physically and chemically distinct from the known art of liposome-type lipid vesicles and from the known art of microemulsions in which surfactants or synthetic emulsifiers comprise a large proportion of the composition. In terms of chemical composition, the particles are somewhat similar to classical emulsions, but due to the finely divided particulate nature of the current invention, a significantly enhanced dermal penetration is achieved. We have thus termed these droplets as submicron emulsion oil spheres.

Insoluble drugs or cosmetically active substances may be dispersed in an aqueous medium as solid or liquid particles to form a suspension. One aspect of this

invention relates to drugs or cosmetically active substances that are liquid at room temperature and may be dispersed as liquid, water-insoluble droplets with the desired droplet size range. Otherwise, for drugs or cosmetics which are solid at room temperature and in the shape of powder or crystals, mixtures with an oil are a preliminary required step in order to obtain oily droplets in aqueous suspension.

An emulsion is a dispersion of oil in water ("o/w"), and can be defined as either a macroemulsion or a microemulsion. A macroemulsion is a cloudy turbid composition having an oil-droplet size of 0.5 to 100 μm and is generally thermodynamically unstable. In comparison, a microemulsion is a translucent to transparent composition having a droplet size of 0.005 to 0.5 μm, is thermodynamically stable and is generally self emulsifying. See, e.g., Friberg et al. (1987) Microemulsions Structure and Dynamics, CRC Press Inc., Boca Raton, FL, pp. 154. Also, the proportion of surfactants to oil required to generate microemulsions is generally much higher than in macroemulsions.

The term "submicron" is used herein to mean a size of about 0.05 to 0.5 μm, and preferably about 0.1 to 0.3 μm. Thus, submicron droplets of these sizes would be smaller than those of a classical macroemulsion, which has droplet sizes of above about 0.5 μm, but generally larger than those of a classical microemulsion, which, for practical purposes, has droplet sizes of less than about 0.1 μm.

These submicron droplets can easily be sterilized by filtration, for example, in 0.45 μm and/or 0.22 μm filters, are more stable in long-term storage and can better withstand sterilization in an autoclave.

An oil-in-water emulsion is a dispersion of droplets or colloidal particles in an aqueous medium, with the colloid particles having an oily core surrounded by an interfacial film of the emulsifiers and surface acting

agents or surfactants. For clarity in understanding the present invention, the following terms will be used:

"aqueous phase" - to denote the aqueous solution in which the droplets or colloid particles are dispersed;

"oily phase" - to denote the oily cores of the droplets or colloidal particles; and

"amphiphilic phase" - to denote the interfacial films of emulsifier and surfactant surrounding the oily phase of the droplets or colloidal particles.

In this invention, the oil may be a vegetable oil, a mineral oil, a medium chain triglyceride (MCT) oil, i.e., a triglyceride oil in which the carbohydrate chain has 8-12 carbons, or a combination of two or three of such oils. Although MCT oil can be considered as a component of vegetable oil, it is separately identified herein because of its particular utility as a preferred oil for use in the present droplets. In addition, MCT oil is available commercially. Examples of such MCT oils include TCR (trade name of Societe Industrielle des Oleagineaux, France for a mixture of triglycerides wherein about 95% of the fatty acid chains have 8 or 10 carbons) and MIGLYOL 810 or 812 (trade name of Dynamit Nobel, Sweden for a mixed triester of glycerine and of caprylic and capric acids). Examples of vegetable oils include soybean oil, cotton seed oil, olive oil, sesame oil and castor oil. The mineral oils may be natural hydrocarbons or their synthetic analogs. Oily fatty acids, such as oleic acid and linoleic acid, fatty alcohols, such as oleyl alcohol, and fatty esters, such as sorbitan monooleate and sucrose mono- di- or tri-palmitate, can be used as the oil component, although these are not as preferred as the other oils mentioned above. The excipient oil may also be of animal source or any acceptable synthetic substitute therefore.

The amphiphilic phase comprises the emulsifiers and surfactants. Preferred emulsifiers include a phospholipid compound or a mixture of phospholipids. Suitable