

Docket No. 17618CON6 (AP)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Examiner: TBA

Serial No.: TBA

Group Art Unit: TBA

Filed: Herewith

Confirmation No. TBA

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Customer No.: 51957

**PRELIMINARY AMENDMENT**

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

Dear Sir:

Prior to examining the above-referenced application, please amend the specification as described on page 2 of this paper, and please amend the claims as described on pages 3-6 of this paper. Remarks follow on page 7.

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Amendments to the Specification

Please replace page 1, lines 5-10 of the specification filed herewith with the following amended paragraph:

This application is a continuation of copending U.S. Application Serial No. 11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No. 10/927,857, filed August 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which ~~is~~ are incorporated in ~~its~~ their entirety herein by reference.

Please replace page 4, line 25 – page 5, line 3 of the specification filed herewith with the following amended paragraph:

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune medicated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve 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.

Amendments to the claims

The following list of claims will replace all previous versions of claims presented in this application:

1. – 36. (Canceled)

37. (New) A topical ophthalmic emulsion for treating an eye of a human having KCS, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, Pemulen, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in treating KCS.

38. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

39. (New) The topical ophthalmic emulsion of Claim 38, wherein the tonicity agent or the demulcent component is glycerine.

40. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion further comprises a buffer.

41. (New) The topical ophthalmic emulsion of Claim 40, wherein the buffer is sodium hydroxide.

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

43. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

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44. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion comprises Pemulen in an amount of about 0.05% by weight.

45. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight, water, and a buffer.

46. (New) The topical ophthalmic emulsion of Claim 45, wherein the buffer is sodium hydroxide.

47. (New) The topical ophthalmic emulsion of Claim 37, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating KCS, the blood of the human has substantially no detectable concentration of cyclosporin A.

48. (New) The topical ophthalmic emulsion of Claim 42, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

49. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion is as substantially therapeutically effective as an emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

50. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion achieves at least as much therapeutic effectiveness as an emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

51. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to an emulsion that contains only 50% as much castor oil.

52. (New) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events

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in the human, relative to an emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

53. (New) The topical ophthalmic emulsion of Claim 52, wherein the adverse events include side effects.

54. (New) A topical ophthalmic emulsion for treating an eye of a human, wherein the topical ophthalmic emulsion increases tear production in the eye of a human, and wherein the topical ophthalmic emulsion comprises:

- cyclosporin A in an amount of about 0.05% by weight;
- castor oil in an amount of about 1.25% by weight;
- polysorbate 80 in an amount of about 1.0% by weight;
- Pemulen in an amount of about 0.05% by weight;
- a tonicity component or a demulcent component in an amount of about 2.2% by weight;
- a buffer; and
- water.

55. (New) The topical ophthalmic emulsion of Claim 54, wherein the buffer is sodium hydroxide.

56. (New) The topical ophthalmic emulsion of Claim 54, wherein the tonicity component or the demulcent component is glycerine.

57. (New) The topical ophthalmic emulsion of Claim 54, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount to increase tear production, the blood of the human has substantially no detectable concentration of the cyclosporin A.

58. (New) The topical ophthalmic emulsion of Claim 54, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

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59. (New) The topical ophthalmic emulsion of Claim 54, wherein the topical ophthalmic emulsion is effective in treating KCS.

60. (New) A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic emulsion comprising:

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

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

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

Pemulen in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water;

wherein the emulsion is effective in treating KCS.

61. (New) The topical ophthalmic emulsion of Claim 60, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

REMARKS

The applicants have canceled claims 1-36 and have added claims 37-61. Support for the limitations recited in the new claims may be found throughout the specification, and at least at page 4, line 25 – page 5, line 14, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith.

Support for the amendment to the specification at page 4, line 25 – page 5, line 3 may be found, at least, in U.S. Patent Nos. 5,474,979 and 6,254,860, which were previously incorporated by reference in the present application specification at page 1, lines 18-21. The amendment contains no new matter.

The claims of the present application may vary in scope from the claims pursued in the parent applications. To the extent any prior amendments or characterizations of the scope of any claim, or the specification, or referenced art could be construed as a disclaimer of any subject matter supported by the present disclosure, the Applicants hereby rescind and retract such disclaimer.

Specifically, the Applicants would like to bring to the Examiner's attention comments made in the Response filed on June 15, 2009 in U.S. Patent Application Serial No. 10/927,857 (now abandoned) and comments made in the Amendment filed on June 15, 2009 in U.S. Patent Application Serial No. 11/897,177 (currently pending) regarding U.S. Patent No. 5,474,979 and the present application specification. Since these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims.

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.

Respectfully submitted,

/Laura L. Wine/

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Date: August 7, 2013

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## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>				
<b>Filing Date:</b>				
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			
<b>First Named Inventor/Applicant Name:</b>	Andrew Ancheampong			
<b>Filer:</b>	Laura Lee Wine/Lauren Barberena			
<b>Attorney Docket Number:</b>	17618CON6 (AP)			
Filed as Large Entity				
<b>Utility under 35 USC 111(a) Filing Fees</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
<b>Pages:</b>				
<b>Claims:</b>				
Claims in Excess of 20	1202	4	80	320
<b>Miscellaneous-Filing:</b>				
Late Filing Fee for Oath or Declaration	1051	1	140	140



Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>2060</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	16531308
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Ancheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Lauren Barberena
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	07-AUG-2013
<b>Filing Date:</b>	
<b>Time Stamp:</b>	20:55:55
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$2060
RAM confirmation Number	7847
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 1.17 (Patent application and reexamination processing fees)
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<b>File Listing:</b>					
<b>Document Number</b>	<b>Document Description</b>	<b>File Name</b>	<b>File Size(Bytes)/ Message Digest</b>	<b>Multi Part /.zip</b>	<b>Pages (if appl.)</b>
1		17618CON_SPEC.pdf	4360450 9b080e02f8cb41c5b767d994b15dca09f38dd180	yes	34
<b>Multipart Description/PDF files in .zip description</b>					
<b>Document Description</b>		<b>Start</b>	<b>End</b>		
Specification		1	28		
Claims		29	33		
Abstract		34	34		
<b>Warnings:</b>					
<b>Information:</b>					
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<b>Multipart Description/PDF files in .zip description</b>					
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Preliminary Amendment		1	1		
Specification		2	2		
Claims		3	6		
Abstract		7	7		
<b>Warnings:</b>					
<b>Information:</b>					

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<b>Information:</b>					
<b>Total Files Size (in bytes):</b>				7953236	
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					

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<b>Filer:</b>	Laura Lee Wine/Lauren Barberena
<b>Filer Authorized By:</b>	Laura Lee Wine
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<b>Warnings:</b>					
<b>Information:</b>					
3	Power of Attorney	17618CON6_POA.pdf	1941040 4dc63f966f017f05a762e232da2f75a00a566a99	no	2
<b>Warnings:</b>					
<b>Information:</b>					
4		17618CON6_PRELIM_AMENDMENT.pdf	107862 e610131ed6a315d56a204abe785b66f7bb776cbb	yes	7
<b>Multipart Description/PDF files in .zip description</b>					
<b>Document Description</b>		<b>Start</b>	<b>End</b>		
Preliminary Amendment		1	1		
Specification		2	2		
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<b>Warnings:</b>					
<b>Information:</b>					

5	Fee Worksheet (SB06)	fee-info.pdf	38503 8572f23d9261a346d3b9f54eaaac4b2c84e9bb	no	2
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>				7953236	
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					

METHODS OF PROVIDING THERAPEUTIC EFFECTS  
USING CYCLOSPORIN COMPONENTS

5 Related Application

This application is a continuation of U.S. Application Serial No. 10/927,857, filed August 27, 2004, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which is incorporated in its  
10 entirety herein by reference.

Background of the Invention

The present invention relates to methods of providing desired therapeutic effects to humans or animals using  
15 compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a  
20 desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S. Patent 6,254,860; and Garst U.S.  
25 6,350,442, this disclosure of each of which is incorporated in its entirety herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "Blood  
30 concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of



cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999 Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "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. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2%

by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if  
5 reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with  
10 cyclosporin-containing emulsions.

#### Summary of the Invention

New methods of treating a human or animal using cyclosporin component-containing emulsions have been  
15 discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for  
20 reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug  
25 interactions. The present methods can be easily practiced.

In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present  
30 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.

5           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  
10 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  
15 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. Additionally, and importantly, using reduced  
20 amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

          In short, the present invention provides at least one advantageous benefit, and preferably a plurality of  
25 advantageous benefits.

          The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is  
30 relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome,

phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

5       Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable  
10 concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

15       In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

20       Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

25       In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of  
30 some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the

cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components,

polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and

every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

5           These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

#### Detailed Description

10           The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S.  
15 pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is  
20 less than 0.08.

          As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently  
25 useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops  
30 or similar form or other form so as to facilitate such topical administration.

          The present methods have been found to be very

effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

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, 5 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.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result 10 of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the 15 human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations 20 below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. 25 After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3µm pore size C-8 reverse phase high pressure liquid chromatography 30 (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a

turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada).

Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at  $m/z$  425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed.

Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

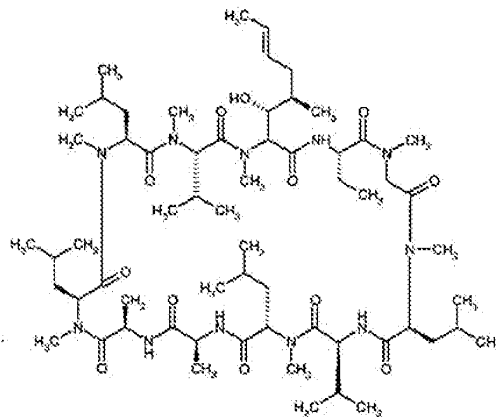
The chemical structure for cyclosporin A is represented by Formula 1

Formula I

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As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-  
 25 (Cyclo)alkylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu)<sup>4</sup>-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-cyclosporin A derivatives described below.

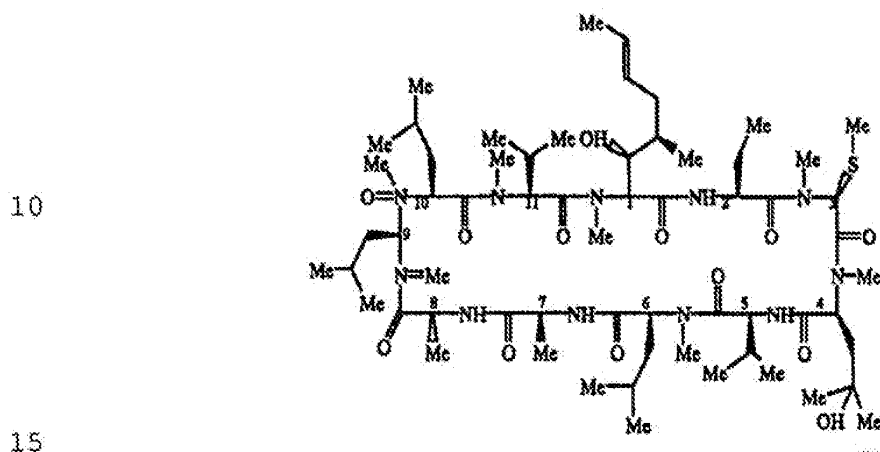
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:  
 30



Formula IV

5

(I)



wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxy carbonyl,  $-NR_1R_2$  or  $N(R_3)-(CH_2)_n-NR_1R_2$ ; wherein  $R_1, R_2$  is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxy carbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or  $NR_1R_2$  is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated;  $R_3$  is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

20

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In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired

30

therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which

have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

5           Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof  
10 are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high  
15 concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

          The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion  
20 compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

25           The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier  
30 components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid

and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives.  
5 Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in  
10 the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or  
15 use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

20 Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or  
25 amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is  
30 nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers



of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

5       The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range  
10 of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

      Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such  
15 components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a  
20 polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-  
25 containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

      A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

30

metal carboxy methylcelluloses  
metal carboxy methylhydroxyethylcelluloses

- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- 5 gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- peptides and polypeptides
- 10 alginic acid
- metal alginates
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - 15 vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - 20 p-styrenesulfonic acid
  - metal p-styrenesulfonate
  - 2-methacryloyloxyethylsulfonic acids
  - metal 2-methacryloyloxethylsulfonates
  - 3-methacryloyloxy-2-hydroxypropylsulfonic acids
  - 25 metal 3-methacryloyloxy-2-hydroxypropylsulfonates
  - 2-acrylamido-2-methylpropanesulfonic acids
  - metal 2-acrylamido-2-methylpropanesulfonates
  - allylsulfonic acid
  - 30 metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component

includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range

of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates,

acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

5 The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like  
10 and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application  
15 involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

20 Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal  
25 chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not  
30 completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by

reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc.

5 An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial  
10 peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and  
15 other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include  
20 viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like);  
25 polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions.  
30 The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the

total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in  
5 producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily  
10 phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid  
15 oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase  
20 is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant  
25 components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is  
30 allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion

concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the  
5 emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter.  
10 Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane  
15 to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform  
20 after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

25 The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room  
30 temperature.

The following non-limiting examples illustrate certain aspects of the present invention.



EXAMPLE 1

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

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
5		
10		
15		

20 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. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to

Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

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 split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be

understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

**WHAT IS CLAIMED IS:**

1. A method of treating an eye of a human or animal comprising:

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.

2. The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. A composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin component to the hydrophobic component being less than 0.08.

22. The composition of claim 21 having a make-up so that when the composition is administered to an eye of a

human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin component.

23. The composition of claim 21 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

24. The composition of claim 21 wherein the cyclosporin component comprises cyclosporin A.

25. The composition of claim 21 in the form of an emulsion.

26. The composition of claim 21 wherein the hydrophobic component is present in an amount greater than 0.625% by weight of the composition.

27. The composition of claim 21 wherein the hydrophobic component is an oily material.

28. The composition of claim 21 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils, and mixtures thereof.

29. The composition of claim 21 wherein the hydrophobic component comprises castor oil.

30. The composition of claim 21 wherein the administering step comprises topically administering the composition to the eye of the human.

31. The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.



METHODS OF PROVIDING THERAPEUTIC EFFECTS  
USING CYCLOSPORIN COMPONENTS

Abstract of the Disclosure

5

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including 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 0.8.

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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

**Secrecy Order 37 CFR 5.2**

Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

**Inventor Information:**

<b>Inventor 1</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Andrew		Acheampong		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	Irvine	<b>State/Province</b>	CA	<b>Country of Residence i</b>	US
<b>Mailing Address of Inventor:</b>					
<b>Address 1</b>	16 Wintergreen				
<b>Address 2</b>					
<b>City</b>	Irvine	<b>State/Province</b>	CA		
<b>Postal Code</b>	92604	<b>Country i</b>	US		
<b>Inventor 2</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Diane	D.	Tang-Liu		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	Las Vegas	<b>State/Province</b>	NV	<b>Country of Residence i</b>	US
<b>Mailing Address of Inventor:</b>					
<b>Address 1</b>	3726 Las Vegas Blvd S. Unit 3303 W				
<b>Address 2</b>					
<b>City</b>	Las Vegas	<b>State/Province</b>	NV		
<b>Postal Code</b>	89158	<b>Country i</b>	US		
<b>Inventor 3</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	James	N.	Chang		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					

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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)		
		Application Number			
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS				
City	Newport Beach	State/Province	CA	Country of Residence i	US
<b>Mailing Address of Inventor:</b>					
Address 1	36 Cervantes				
Address 2					
City	Newport Beach	State/Province	CA		
Postal Code	92660	Country i	US		
Inventor 4					<input type="button" value="Remove"/>
<b>Legal Name</b>					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	David	F.	Power		
<b>Residence Information (Select One)</b> <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Hubert	State/Province	NC	Country of Residence i	US
<b>Mailing Address of Inventor:</b>					
Address 1	202 Fox Way N				
Address 2					
City	Hubert	State/Province	NC		
Postal Code	28539	Country i	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					<input type="button" value="Add"/>

**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
<input type="checkbox"/> An Address is being provided for the correspondence Information of this application.			
Customer Number	51957		
Email Address	patents_ip@allergan.com	<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

**Application Information:**

Title of the Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
Attorney Docket Number	17618CON6 (AP)	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

**Publication Information:**

Request Early Publication (Fee required at time of Request 37 CFR 1.219)

**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

**Representative Information:**

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	51597		

**Domestic Benefit/National Stage Information:**

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending	<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	11897177	2007-08-28
Prior Application Status	Abandoned	<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	10927857	2004-08-27
Prior Application Status	Expired	<a href="#">Remove</a>	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	60503137	2003-09-15
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the <b>Add</b> button.			<a href="#">Add</a>

**Foreign Priority Information:**

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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country <sup>i</sup>	Filing Date (YYYY-MM-DD)	Access Code <sup>i</sup> (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

- This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

## Authorization to Permit Access:

Authorization to Permit Access to the Instant Application by the Participating Offices

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

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
<b>Applicant 1</b>			<input type="button" value="Remove"/>
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
			<input type="button" value="Clear"/>
<input checked="" type="radio"/> Assignee	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Joint Inventor	
<input type="radio"/> Person to whom the inventor is obligated to assign.		<input type="radio"/> Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor : <input type="text"/>			
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	Allergan, Inc.		
<b>Mailing Address Information:</b>			
Address 1	2525 Dupont Drive		
Address 2			
City	Irvine	State/Province	CA
Country <sup>i</sup>	US	Postal Code	92612
Phone Number		Fax Number	

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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
Email Address	patent_ip@allergan.com		
Additional Applicant Data may be generated within this form by selecting the Add button.			<input type="button" value="Add"/>

**Non-Applicant Assignee Information:**

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.				
<b>Assignee 1</b>				
Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).				
				<input type="button" value="Remove"/>
If the Assignee is an Organization check here. <input type="checkbox"/>				
Prefix	Given Name	Middle Name	Family Name	Suffix
<b>Mailing Address Information:</b>				
Address 1				
Address 2				
City		State/Province		
Country i		Postal Code		
Phone Number		Fax Number		
Email Address				
Additional Assignee Data may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

**Signature:**

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications				
Signature	/Laura L. Wine/		Date (YYYY-MM-DD)	2013-08-07
First Name	Laura	Last Name	Wine	Registration Number
				68681
Additional Signature may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

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

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	17618CON6 (AP)
		Application Number	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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 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.

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**TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE  
REGISTERED PRACTITIONERS**

**NOTE:** This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	unknown
Filing Date	herewith
First Named Inventor	Andrew Acheampong
Title	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
Art Unit	
Examiner Name	
Attorney Docket Number	17618CON6 (AP)

**SIGNATURE of Applicant or Patent Practitioner**

Signature	/Laura L. Wine/	Date	August 7, 2013
Name	Laura L. Wine	Telephone	714-246-6996
Registration Number	68,681		

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications.

\*Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, 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.*

## POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

51957

**OR**

I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number	Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

The address associated with the above-mentioned Customer Number.

**OR**

The address associated with Customer Number:

**OR**

Firm or Individual Name

Address

City

State

Zip

Country

Telephone

Email

I am the Applicant:

Inventor or Joint Inventor

Legal Representative of a Deceased or Legally Incapacitated Inventor

Assignee or Person to Whom the Inventor is Under an Obligation to Assign

Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

### SIGNATURE of Applicant for Patent

Signature

Date

Name

Debra D. Condino, Reg. No. 31,007

Telephone

714-246-2388

Title and Company

Assistant Secretary, Allergan, Inc.

**NOTE:** Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below \*.

\*Total of \_\_\_\_\_ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, 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.*

Document code: WFEE

United States Patent and Trademark Office  
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MTEKLEMI	SALE	#00000029	Mailroom Dt:	08/07/2013	010885	13961828
		01	FC : 1202	80.00	DA	

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875			Application or Docket Number <b>13/961,828</b>	Filing Date <b>08/07/2013</b>	<input type="checkbox"/> To be Mailed
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO					
<b>APPLICATION AS FILED – PART I</b>					
(Column 1)		(Column 2)			
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =		
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		

<b>APPLICATION AS AMENDED – PART II</b>								
(Column 1)		(Column 2)		(Column 3)				
<b>AMENDMENT</b>	<b>08/07/2013</b>	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 25	Minus	** 25	= 0	X \$80 =	0	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$420 =	0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))							
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
						TOTAL ADD'L FEE	<b>0</b>	

(Column 1)		(Column 2)		(Column 3)				
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =		
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))							
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
						TOTAL ADD'L FEE		
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.                  ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".                  *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".                  The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>						LIE /SHERRY DAVIS/		

This collection of information is required by 37 CFR 1.16. 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, 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.**  
 If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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**SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY  
OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)**

Title of Invention	Methods of Providing Therapeutic Effects Using Cyclosporin Components Docket No.: 17618CON6(AP)						
This statement is directed to:							
<input type="checkbox"/> The attached application,							
OR							
<input checked="" type="checkbox"/> United States application or PCT International application number <u>13/961,828</u> filed on <u>8-7-13</u>							
LEGAL NAME of inventor to whom this substitute statement applies:							
(E.g., Given Name (first and middle (if any)) and Family Name or Surname)							
James N. Chang							
Residence (except for a deceased or legally incapacitated inventor):							
City	Newport Beach	State	CA	Country	US		
Mailing Address (except for a deceased or legally incapacitated inventor):							
36 Cervantes							
City	Newport Beach	State	CA	Zip	92660	Country	US
I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.							
The above-identified application was made or authorized to be made by me.							
I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.							
Relationship to the inventor to whom this substitute statement applies:							
<input type="checkbox"/> Legal Representative (for deceased or legally incapacitated inventor only),							
<input checked="" type="checkbox"/> Assignee,							
<input type="checkbox"/> Person to whom the inventor is under an obligation to assign,							
<input type="checkbox"/> Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.48 is required), or							
<input type="checkbox"/> Joint Inventor.							

[Page 1 of 2]

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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**SUBSTITUTE STATEMENT**

## Circumstances permitting execution of this substitute statement:

- Inventor is deceased,
- Inventor is under legal incapacity,
- Inventor cannot be found or reached after diligent effort, or
- Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

- An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

## PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: **Debra D. Condino** TITLE: ASSISTANT SECRETARY (ASSIGNEE)  
COMPANY: ALLERGAN, INC. (Date Optional)

Signature: *D Condino*

Residence (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	Irvine	State	CA	Country	US
------	--------	-------	----	---------	----

Mailing Address (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

2525 Dupont Drive-T2-7H

City	Irvine	State	CA	Zip	92612	Country	US
------	--------	-------	----	-----	-------	---------	----

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

## 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.



**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**

<b>Title of Invention</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS Docket No.: 17618CON6(AP)
---------------------------	--

As the below named inventor, I hereby declare that:

This declaration is directed to:  The attached application, or  
 United States application or PCT international application number 13/961,828  
 filed on 8/7/2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

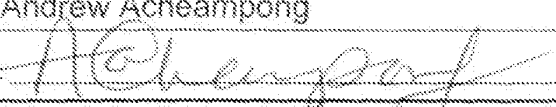
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Andrew Acheampong Date (Optional): \_\_\_\_\_

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 116 and 37 CFR 1.63. 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 1 minute 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 1480, Alexandria, VA 22313-1480. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.  
 If you need assistance in completing this form, call 1-800-PTO-9198 and select option 2.

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## DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of  
Invention

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN  
COMPONENTS  
Docket No.: 17618CON6(AP)

As the below named inventor, I hereby declare that:

This declaration  
is directed to:

The attached application, or

United States application or PCT international application number 13/961,828filed on 8/7/2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

**WARNING:**

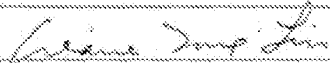
Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: DIANE TANG-LIU

Date (Optional): \_\_\_\_\_

Signature: \_\_\_\_\_



Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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 1458, Alexandria, VA 22313-1458. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1458, Alexandria, VA 22313-1458.

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

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**

<b>Title of Invention</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS Docket No.: 17618CON6(AP)
---------------------------	--

As the below named inventor, I hereby declare that:

This declaration is directed for:  The attached application, or  United States application or PCT international application number 13/961,828 filed on 8/7/2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: DAVID F. POWER Date (Optional): 8-12-2013

Signature: *David F. Power*

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entry, must accompany this form. Use an additional PTO/SB/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 110 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to be sent 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 1 minute 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 1480, Alexandria, VA 22313-1480. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.  
If you need assistance in completing this form, call 1-800-PTO-6100 and select option 3.

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	13961828			
<b>Filing Date:</b>				
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong			
<b>Filer:</b>	Laura Lee Wine/Bonnie Ferguson			
<b>Attorney Docket Number:</b>	17618CON6 (AP)			
Filed as Large Entity				
<b>Utility under 35 USC 111(a) Filing Fees</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
Late Filing Fee for Oath or Declaration	1051	1	140	140
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>140</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	16592820
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Bonnie Ferguson
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	14-AUG-2013
<b>Filing Date:</b>	
<b>Time Stamp:</b>	17:53:37
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$140
RAM confirmation Number	5452
Deposit Account	010885
Authorized User	

### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1	Oath or Declaration filed	substitutestatementcon6-8-14-13.pdf	278513 cf5f723bc64da09fac881303f7008f673f13dca6	no	3
<b>Warnings:</b>					
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					
<b>Information:</b>					
2	Oath or Declaration filed	SignedDec17618CON6-8-14-13b.pdf	515783 9ed599431f115f7c73531ecd2e40c5e8a4e4990	no	3
<b>Warnings:</b>					
<b>Information:</b>					
3	Fee Worksheet (SB06)	fee-info.pdf	30596 8f39b5b61df93774ccb8180ffe516a03d8987ed	no	2
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>			824892		
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					

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Seq No: 5452 Sales Acctg Dt: 08/15/2013 010885 13961828  
01 FC : 1051 140.00 CR



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Serial No.: 13/961,828

Filed: August 7, 2013

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Examiner: TBA

Group Art Unit: 1653

Confirmation No. 9904

Customer No.: 51957

**SUBMISSION OF SUBSTITUTE SPECIFICATION**

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

The Applicants file with this paper 1) a substitute specification, marked to show changes against the specification filed on August 7, 2013; and 2) a clean version of the specification, incorporating those changes in compliance with 37 CFR 1.125(c). The applicants have revised the specification to show the changes made by the preliminary amendment filed on August 7, 2013; they have not added any new matter. Please replace the specification (excluding the claims) of the above-referenced application with the substitute specification.

As stated in the preliminary amendment filed on August 7, 2013, support for the amendment to the specification at page 4, line 25 – page 5, line 3 of the specification filed August 7, 2013, which correspond to page 3, line 25 – page 4, line 3 of the substitute and clean specifications filed herewith, may be found, at least, in U.S. Patent Nos. 5,474,979 and 6,254,860, which were previously incorporated by reference in the present application specification at page 1, lines 18-21. The amendment contains no new matter.

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.

Respectfully submitted,

/Laura L. Wine/

---

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

Date: August 26, 2013

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

**METHODS OF PROVIDING THERAPEUTIC EFFECTS**  
**USING CYCLOSPORIN COMPONENTS**

**Related Application**

5 This application is a continuation of copending U.S. Application Serial No. 11/897,177,  
filed August 28, 2007, which is a continuation of U.S. Application Serial No. 10/927,857, filed  
August 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No.  
60/503,137 filed September 15, 2003, which are incorporated in their entirety herein by  
reference.

10

**Background of the Invention**

The present invention relates to methods of providing desired therapeutic effects to  
humans or animals using compositions including cyclosporin components. More particularly,  
the invention relates to methods including administering to an eye of a human or animal a  
15 therapeutically effective amount of a cyclosporin component to provide a desired therapeutic  
effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions  
has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S.  
Patent 6,254,860; and Garst U.S. 6,350,442, this disclosure of each of which is incorporated in  
20 its entirety herein by reference. In addition, cyclosporin A compositions used in treating  
ophthalmic conditions is the subject of a number of publications. Such publications include, for  
example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a  
ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul  
Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after  
25 topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999  
Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and  
systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes,"  
Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of  
cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5;  
30 "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74;  
and "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. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

### **Summary of the Invention**

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

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  
5 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  
10 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. Additionally, and importantly, using reduced  
15 amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically  
20 sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is  
25 particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production  
30 (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve 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.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an

amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more

of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

5

**Detailed Description**

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are



ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

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.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

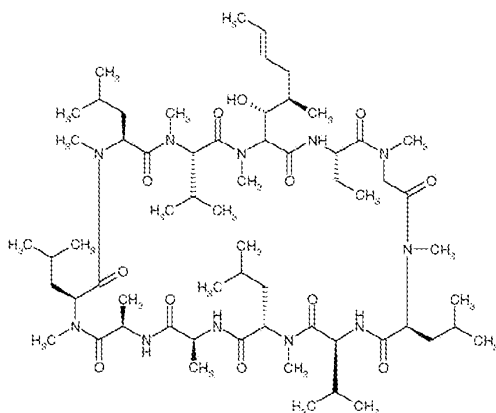
One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3 $\mu$ m pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the

analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

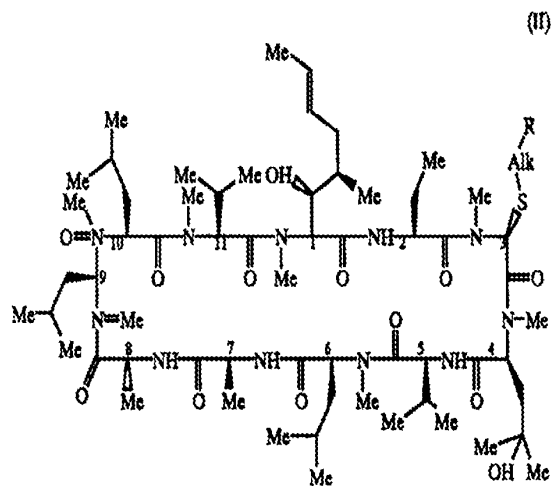
**Formula 1**



As used herein the term “derivatives” of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu)<sup>4</sup>-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-cyclosporin A derivatives described below.

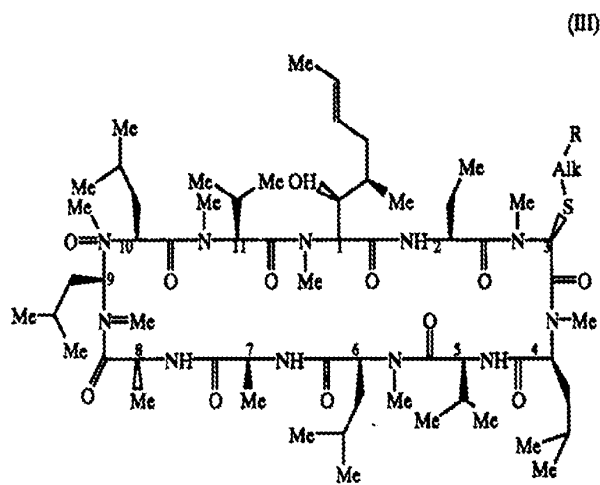
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

**Formula II**



5

**Formula III**



10

**Formula IV**



considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

5 In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

10 Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

20 The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

30 The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components,

preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained  
5 in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

10 In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components  
15 include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphotheric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include,  
20 without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present  
25 emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently  
30 useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the

emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing  
5 polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- 10 metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- 15 heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- 20 peptides and polypeptides
- alginate acid
- metal alginates
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - 25 metal acrylates and methacrylates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - 30 p-styrenesulfonic acid
  - metal p-styrenesulfonate

2-methacryloyloxyethylsulfonic acids  
metal 2-methacryloyloxethylsulfonates  
3-methacryloyloxy-2-hydroxypropylsulfonic acids  
metal 3-methacryloyloxy-2-  
5 hydroxypropylsulfonates  
2-acrylamido-2-methylpropanesulfonic acids  
metal 2-acrylamido-2-methylpropanesulfonates  
allylsulfonic acid  
metal allylsulfonate and the like.

10

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials  
15 include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the  
20 presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02%  
25 by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without  
30 limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being



isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about

0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after

filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions.

5 The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

**EXAMPLE 1**

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

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
Cyclosporin	0.1	0.05
15 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
20 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

25 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  
 30 that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the

amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

5 Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

10 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 split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

15 Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

20 While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

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**METHODS OF PROVIDING THERAPEUTIC EFFECTS****USING CYCLOSPORIN COMPONENTS****Related Application**

5 This application is a continuation of copending U.S. Application Serial No. 11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No. 10/927,857, filed August 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which-is are incorporated in ~~its~~ their entirety herein by reference.

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**Background of the Invention**

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

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The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S. Patent 6,254,860; and Garst U.S. 6,350,442, this disclosure of each of which is incorporated in its entirety herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul Pharmacol Ther*, 2002 Oct, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res*, 1999 Feb, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "Preclinical safety studies of cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic

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emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group,” Sall et al, *Ophthalmology*, 2000 Apr, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

**Summary of the Invention**

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

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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. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporins is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve to correct corneal and



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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.

Employing reduced concentrations of cyclosporin component, as in the present invention,  
5 is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

10 In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites,  
15 cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or  
20 configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A,  
25 derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently  
30 useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an

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amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

5 Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

10 The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the  
15 presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to  
20 be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into  
25 contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

30 The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more

of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

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**Detailed Description**

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are

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ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

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.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3µm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the

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analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and

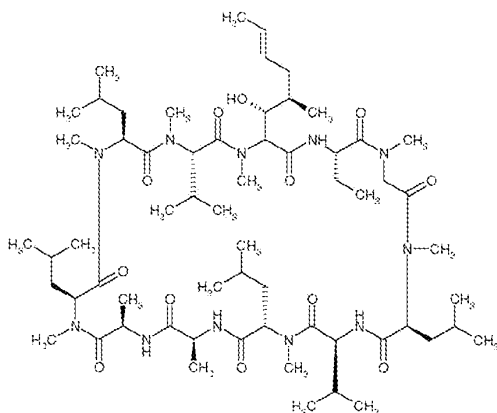
5 deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

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**Formula 1**



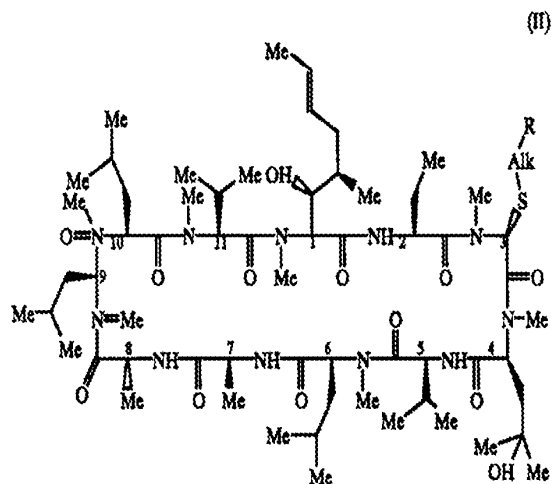
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As used herein the term “derivatives” of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu)<sup>4</sup>-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-cyclosporin A

20 derivatives described below.

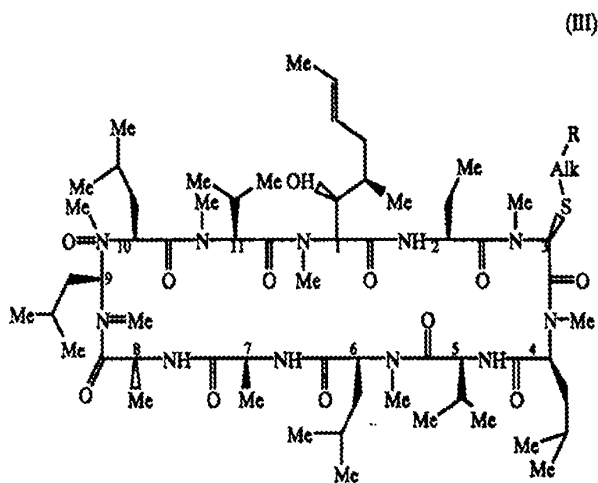
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

**Formula II**



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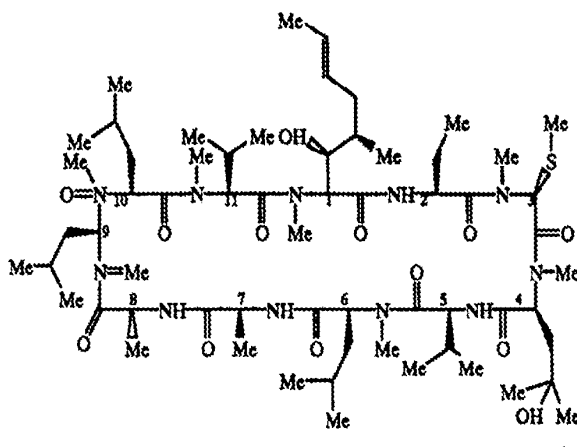
**Formula III**



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**Formula IV**

(I)



wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxy carbonyl,  $-NR_1R_2$  or  $N(R_3)C(CH_2)_nCNR_1R_2$ ; wherein  $R_1, R_2$  is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxy carbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or  $NR_1R_2$  is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated;  $R_3$  is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

10 In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

15 One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

20 Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being

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considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

5 In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally  
10 occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty  
15 acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more  
20 therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about  
25 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation,  
30 emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components,



preservative components and the like.

5 In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

10 In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphoterteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

25 The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

30 Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the

emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- 10 metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- 15 heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- 20 peptides and polypeptides
- alginate acid
- metal alginates
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - 25 metal acrylates and methacrylates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - 30 p-styrenesulfonic acid
  - metal p-styrenesulfonate

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2-methacryloyloxyethylsulfonic acids  
metal 2-methacryloyloxethylsulfonates  
3-methacryloyloxy-2-hydroxypropylsulfonic acids  
metal 3-methacryloyloxy-2-  
5 hydroxypropylsulfonates  
2-acrylamido-2-methylpropanesulfonic acids  
metal 2-acrylamido-2-methylpropanesulfonates  
allylsulfonic acid  
metal allylsulfonate and the like.

10

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials  
15 include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the  
20 presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02%  
25 by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without  
30 limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being

isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about

0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

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The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after

filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions.

- 5 The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

### EXAMPLE 1

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

	<u>Composition I</u>	<u>Composition II</u>
	wt%	wt%
Cyclosporin	0.1	0.05
15 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
20 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

- 25 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  
30 that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the

## SUBSTITUTE SPECIFICATION - MARKED-UP COPY

amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

5 Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

10 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 split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

15 Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

20 While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.



## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	16688694
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Bonnie Ferguson
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	26-AUG-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	17:19:58
<b>Application Type:</b>	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	Applicant Response to Pre-Exam Formalities Notice	17618CON6COVERLETTERFOR UBSPEC.pdf	103528  d04a6a6aec7f835a7e162b743339d9fff6e26451	no	2

### Warnings:

### Information:

2	Specification	17618CLEANCOPYSPEC-CON6.pdf	493818 6259316f4154add895072cf5c3a79f78ef086135	no	19
<b>Warnings:</b>					
<b>Information:</b>					
3	Specification	17618CON6MARKEDUPSPEC.pdf	495990 c09b27ed415177191f93dc9d79d4d66329fef969	no	19
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>				1093336	
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					



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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY. DOCKET NO, TOT CLAIMS, IND CLAIMS. Row 1: 13/961,828, 08/07/2013, 1653, 2140, 17618CON6 (AP), 25, 3

CONFIRMATION NO. 9904

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

FILING RECEIPT



Date Mailed: 08/28/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections

Inventor(s)

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, NV;
James N. Chang, Newport Beach, CA;
David F. Power, Hubert, NC;

Applicant(s)

Allergan, Inc., Irvine, CA

Assignment For Published Patent Application

Allergan, Inc., Irvine, CA

Power of Attorney: The patent practitioners associated with Customer Number 51957

Domestic Priority data as claimed by applicant

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

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper Authorization to Permit Access to Application by Participating Offices (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 08/22/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/961,828**

**Projected Publication Date:** To Be Determined - pending completion of Corrected Papers

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

**Preliminary Class**

435

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

### **PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES**

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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**Title 37, Code of Federal Regulations, 5.11 & 5.15**

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number 13/961,828
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APPLICATION AS FILED - PART I			SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	(Column 1)	(Column 2)					
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A			N/A	280
SEARCH FEE <small>(37 CFR 1.16(k), (l), or (m))</small>	N/A	N/A	N/A			N/A	600
EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	25	minus 20 = *	5		OR	x 80 =	400
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	3	minus 3 = *				x 420 =	0.00
APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2000

APPLICATION AS AMENDED - PART II					SMALL ENTITY		OR	OTHER THAN SMALL ENTITY		
	(Column 1)	(Column 2)	(Column 3)							
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=		OR	x	=	
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=		OR	x	=	
	Application Size Fee <small>(37 CFR 1.16(s))</small>							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE		
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=		OR	x	=	
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=		OR	x	=	
	Application Size Fee <small>(37 CFR 1.16(s))</small>							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE		
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.</p>										



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/961,828	08/07/2013	Andrew Acheampong	17618CON6 (AP)

**CONFIRMATION NO. 9904**

**POA ACCEPTANCE LETTER**

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



Date Mailed: 08/28/2013

**NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY**

This is in response to the Power of Attorney filed 08/07/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/tqlam/

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



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Table with 4 columns: APPLICATION NUMBER (13/961,828), FILING OR 371(C) DATE (08/07/2013), FIRST NAMED APPLICANT (Andrew Acheampong), ATTY. DOCKET NO./TITLE (17618CON6 (AP))

CONFIRMATION NO. 9904

FORMALITIES LETTER

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



Date Mailed: 08/28/2013

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification excluding claims in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125 is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). Since a preliminary amendment was present on the filing date of the application and such amendment is part of the original disclosure of the application, the substitute specification must include all of the desired changes made in the preliminary amendment. See 37 CFR 1.115 and 1.215.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): Diane D. Tang-Liu

Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.



Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

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Commissioner for Patents  
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/tgebre/

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

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828
	Filing Date		2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code <sup>1</sup>	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1	3278447		1966-10-11	Thomas McNicholas	
	2	4388229		1983-06-14	Cherng-Chyi Fu	
	3	4388307		1983-06-14	Thomas Cavanak	
	4	4614736		1986-09-30	Delevallee et al	
	5	4649047		1987-03-10	Renee Kaswan	
	6	4764503		1988-08-16	Roland Wenger	
	7	4814323		1989-03-21	Andrieu et al	
	8	4839342		1989-06-13	Renee Kaswan	

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828	
	Filing Date		2013-08-07	
	First Named Inventor		ACHEAMPONG, ANDREW	
	Art Unit		1653	
	Examiner Name		TBD	
	Attorney Docket Number		17618-US-CON6-AP	

	9	4970076		1990-11-13	David Horrobin	
	10	4990337		1991-02-05	Kurihara et al	
	11	4996193		1991-02-26	Hewitt et al	
	12	5047396		1991-09-10	Orban et al	
	13	5051402		1991-09-24	Kurihara et al	
	14	5053000		1991-10-01	Booth et al	
	15	5286730		1994-02-15	Caufield et al	
	16	5286731		1994-02-15	Caufield et al	
	17	5294604		1994-03-15	Nussenblatt et al	
	18	5296158		1994-03-22	MacGilp et al	
	19	5342625		1994-08-30	Hauer et al	

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828	
	Filing Date		2013-08-07	
	First Named Inventor		ACHEAMPONG, ANDREW	
	Art Unit		1653	
	Examiner Name		TBD	
	Attorney Docket Number		17618-US-CON6-AP	

	20	5368854		1994-11-29	Donna Rennick	
	21	5411952		1995-05-02	Renee Kaswan	
	22	5424078		1995-06-13	Anthony Dziabo	
	23	5474919		1995-12-12	Chartrain et al	
	24	5474979		1995-12-12	Ding et al	U.S. Application No. 08/243,279 and its entire prosecution history**
	25	5504068		1996-04-02	Komiya et al	
	26	5540931		1996-07-30	Hewitt et al	
	27	5543393		1996-08-06	Kim et al	
	28	5589455		1996-12-31	Jong Woo	
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49	SALL, KENNETH ET AL, Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, Ophthalmology, 2000, 631-639, 107	<input type="checkbox"/>
50	SANDBORN, WILLIAM ET AL, A Placebo-Controlled Trial of Cyclosporine Enemas for Mildly to Moderately Active Left-Sided Ulcerative Colitis, Gastroenterology, 1994, 1429-1435, 106	<input type="checkbox"/>
51	SANDBORN, WILLIAM ET AL, Cyclosporine Enemas for Treatment-Resistant, Mildly to Moderately Active, Left-Sided Ulcerative Colitis, American Journal of Gastroenterology, 1993, 640-645, 88(5)	<input type="checkbox"/>

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	Filing Date	2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

52	SCHWAB, MATTHIAS ET AL, Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel Disease, Clin Pharm, 2001, 723-751, 60(10)	<input type="checkbox"/>
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828
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	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

63	VAN DER REIJDEN, WILLY ET AL, Treatment of Oral Dryness Related Complaints (Xerostomia) in Sjogren's Syndrome, Ann Rheum Dis, 1999, 465-473, 58	<input type="checkbox"/>
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<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Ken Dinh
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	05-SEP-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	20:50:46
<b>Application Type:</b>	Utility under 35 USC 111(a)

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<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  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.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  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.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  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.</p>					

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	16778458
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Ken Dinh
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	05-SEP-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	20:58:14
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	RudingerPeptideHormones1_7_1976.pdf	2488192 <small>b6fc18b6ad98c34de41f2d461a1f5736500be985</small>	no	11

### Warnings:

### Information:

2	Non Patent Literature	Sall_2000.pdf	208829	no	9
			065c18613831a6d2cfa88066e70ae03daae1b29		
<b>Warnings:</b>					
<b>Information:</b>					
3	Non Patent Literature	SandbornGastroenterology1429_1435_1994.pdf	872000	no	7
			730e8bcd0c58076ab6f0163f4551eff0f507e5c6		
<b>Warnings:</b>					
<b>Information:</b>					
4	Non Patent Literature	Sandborn_1993.pdf	1969241	no	6
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<b>Warnings:</b>					
<b>Information:</b>					
5	Non Patent Literature	SchwabPharmacokinet723_751_2001.pdf	4260474	no	30
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<b>Information:</b>					
6	Non Patent Literature	Secchi_1990.pdf	3200224	no	5
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<b>Warnings:</b>					
<b>Information:</b>					
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<b>Information:</b>					
8	Non Patent Literature	Small_2002.pdf	70523	no	8
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<b>Information:</b>					
9	Non Patent Literature	Smilek_1991.pdf	1645292	no	5
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<b>Information:</b>					
10	Non Patent Literature	Stephenson_The_latest_uses_of_Restasis.pdf	2875746	no	7
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<b>Information:</b>					

11	Non Patent Literature	Stevenson_2000.pdf	255058	no	8
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<b>Warnings:</b>					
<b>Information:</b>					
12	Non Patent Literature	TesavibulTopicalCyclosporine1996.pdf	56707	no	1
			fc4bba0a0ff0194e2146e1e1dbb52551410edeb		
<b>Warnings:</b>					
<b>Information:</b>					
13	Non Patent Literature	Medical_Dictionary_2005.pdf	670357	no	6
			2816eb8d1deb894d8911bacd15ed728364426c81		
<b>Warnings:</b>					
<b>Information:</b>					
14	Non Patent Literature	Tibell_Cyclosporin_A_in_Fat_EmulSION_115_121_76.pdf	697241	no	7
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<b>Warnings:</b>					
<b>Information:</b>					
15	Non Patent Literature	Tsubota_1998.pdf	2353818	no	10
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<b>Information:</b>					
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<b>Information:</b>					
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18	Non Patent Literature	13967189.pdf	2596695	no	34
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<b>Information:</b>					
19	Non Patent Literature	13967179.pdf	2596695	no	34
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<b>Warnings:</b>					
<b>Information:</b>					

20	Non Patent Literature	13961818.pdf	2596695	no	34
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21	Non Patent Literature	13961835.pdf	2596695	no	34
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<b>Warnings:</b>					
<b>Information:</b>					
22	Non Patent Literature	13961808.pdf	2596695	no	34
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<b>Warnings:</b>					
<b>Information:</b>					
23	Non Patent Literature	13967163.pdf	2596695	no	34
			597b1bba8cf47cb818eb51c45eca2e943c4 b4463		
<b>Warnings:</b>					
<b>Information:</b>					
24	Non Patent Literature	13967168.pdf	2596695	no	34
			2244ea61fc0c84bfa743e5a148d34b2d6ba 9564e		
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>			43907702		
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number 13/961,828
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APPLICATION AS FILED - PART I			SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	(Column 1)	(Column 2)					
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE <small>(37 CFR 1.16(a), (b), or (c))</small>	N/A	N/A	N/A			N/A	280
SEARCH FEE <small>(37 CFR 1.16(k), (l), or (m))</small>	N/A	N/A	N/A			N/A	600
EXAMINATION FEE <small>(37 CFR 1.16(o), (p), or (q))</small>	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS <small>(37 CFR 1.16(i))</small>	25	minus 20 = *	5			x 80 =	400
INDEPENDENT CLAIMS <small>(37 CFR 1.16(h))</small>	3	minus 3 = *				x 420 =	0.00
APPLICATION SIZE FEE <small>(37 CFR 1.16(s))</small>	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT <small>(37 CFR 1.16(j))</small>							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2000

APPLICATION AS AMENDED - PART II					SMALL ENTITY		OR	OTHER THAN SMALL ENTITY		
	(Column 1)	(Column 2)	(Column 3)							
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=			x	=	
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=			x	=	
	Application Size Fee <small>(37 CFR 1.16(s))</small>									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>									
					TOTAL ADD'L FEE			TOTAL ADD'L FEE		
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)	
	Total <small>(37 CFR 1.16(i))</small>	*	Minus	**	=			x	=	
	Independent <small>(37 CFR 1.16(h))</small>	*	Minus	***	=			x	=	
	Application Size Fee <small>(37 CFR 1.16(s))</small>									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <small>(37 CFR 1.16(j))</small>									
					TOTAL ADD'L FEE			TOTAL ADD'L FEE		
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.</p>										



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/961,828	08/07/2013	Andrew Acheampong	17618CON6 (AP)

**CONFIRMATION NO. 9904**

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

**NOTICE**



Date Mailed: 09/10/2013

**INFORMATIONAL NOTICE TO APPLICANT**

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):  
Diane D. Tang-Liu  
Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.



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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY.DOCKET.NO, TOT CLAIMS, IND CLAIMS. Row 1: 13/961,828, 08/07/2013, 1653, 2140, 17618CON6 (AP), 25, 3

CONFIRMATION NO. 9904

UPDATED FILING RECEIPT



\*OC00000063577077\*

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

Date Mailed: 09/10/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections

Inventor(s)

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, NV;
James N. Chang, Newport Beach, CA;
David F. Power, Hubert, NC;

Applicant(s)

Allergan, Inc., Irvine, CA

Assignment For Published Patent Application

Allergan, Inc., Irvine, CA

Power of Attorney: The patent practitioners associated with Customer Number 51957

Domestic Priority data as claimed by applicant

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

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper Authorization to Permit Access to Application by Participating Offices (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 08/22/2013



The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/961,828**

**Projected Publication Date:** 12/19/2013

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

**Preliminary Class**

435

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

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**Title 37, Code of Federal Regulations, 5.11 & 5.15**

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Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828
	Filing Date	2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code <sup>1</sup>	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828
	Filing Date	2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

	1	U.S. Re-Examination Application: 90/009,944 and its entire prosecution history, Filed on August, 27, 2011 **	<input type="checkbox"/>
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**EXAMINER SIGNATURE**

Examiner Signature		Date Considered	
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\*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.

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

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828
	Filing Date	2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

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

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**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).

\*\* Signature indicates consideration of publication and file history. The Examiner has access to these materials through the PTO computer systems. If additional copies are desired, please notify the Applicants through their attorneys.

- 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)	2013-09-25
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 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.

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	16952193
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Ken Dinh
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	25-SEP-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	14:21:49
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### 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)	17618CON6-IDS_09_25_2013.pdf	493634 <small>b5c8dcb5b5d9a65e6d8c8ce102254ed54bfc353</small>	no	4

### Warnings:

### Information:

This is not an USPTO supplied IDS fillable form

2	Non Patent Literature	90009944.pdf	1904560	no	39
			4b5aa1ab68a1940d5930d4265e9053cf67203dc9		

**Warnings:**

**Information:**

<b>Total Files Size (in bytes):</b>	2398194
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**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.**



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.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**

<b>Title of Invention</b>	<b>METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS</b>
-------------------------------	--

As the below named inventor, I hereby declare that:

This declaration is directed to:  The attached application, or  
 United States application or PCT international application number \_\_\_\_\_  
filed on \_\_\_\_\_.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

**LEGAL NAME OF INVENTOR**

Inventor: Diane D. Tang-Liu Date (Optional) : \_\_\_\_\_  
Signature: *Diane Tang-Liu*

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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.

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

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	17067912
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Alexis Swan
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	08-OCT-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	13:36:48
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	17618-Tang-Liu-Declaration.pdf	115996 e6cccf12c8997e0cd437abb948b1271c3c3b1e2	no	1

### Warnings:

### Information:

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**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

Table with columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO., EXAMINER, ART UNIT, PAPER NUMBER, NOTIFICATION DATE, DELIVERY MODE. Includes application details for Andrew Acheampong and examiner Marcela M. Cordero Garcia.

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



### **DETAILED ACTION**

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

#### ***Election/Restrictions***

This application contains claims directed to the following patentably distinct species: the many and multiple tonicity or demulcent agents, the many and multiple buffers to be used in the instantly claimed topical ophthalmic composition. The species are independent or distinct because each tonicity agent, demulcent agent and buffer corresponds to different physical and molecular compositions with different biochemical and biophysical properties, different pH, different solubility, different reactivity and so forth. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species [i.e., elect a single and specific tonicity and/or demulcent agent, and elect a single and specific buffer], for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 37-61 are generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: a reference that would anticipate and/or make obvious one of the species would not necessarily anticipate and/or make obvious another species.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

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.



Application/Control Number: 13/961,828  
Art Unit: 1658

Page 5

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

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

MMCG 10/2013

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Andrew Acheampong et al.

Examiner: Marcela M. Cordero Garcia

Serial No.: 13/961,828

Art Unit: 1658

Filed: August 7, 2013

Confirmation No.: 9904

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Docket No.: 17618CON6 (AP)

**RESPONSE TO RESTRICTION REQUIREMENT**

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

Dear Sir:

These papers are filed in reply to the Restriction Requirement mailed October 25, 2013.

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 dated October 25, 2013.

**Species Election**

In response to the requirement for an election of species, the Applicants hereby provisionally elect the following species for examination, with traverse:

- a) Tonicity agent or demulcent component: glycerine (Claims 38, 54, 55, 57, 58, 59)
- b) Buffer: sodium hydroxide (Claims 40, 42, 45, 48, 54, 56, 57, 58, 59)

The Applicants hereby traverse the requirement for an election of species with respect to Claims 37-61. The Applicants submit that the species identified by the Examiner does not require an additional searching burden on the Office, and that the requirement for a species election is improper under the MPEP.

The Applicants also reserve the right to have the unelected species considered once the Examiner finds the elected species allowable.

Should the Examiner wish to discuss these or any other issues, please contact Laura L. Wine at (714)246-6996.

Respectfully submitted,

Date: December 2, 2013

/Laura L. Wine/

Laura L. Wine  
Registration Number 68,681



**ALLERGAN**

**LEGAL DEPARTMENT**

2525 Dupont Drive

Irvine, California 92612-1599 Tel: 714/246-6996 Fax: 714/246-4249

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	13961828
<b>Filing Date:</b>	07-Aug-2013
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Filer:</b>	Laura Lee Wine/Alexis Swan
<b>Attorney Docket Number:</b>	17618CON6 (AP)

Filed as Large Entity

### Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				
Extension - 1 month with \$0 paid	1251	1	200	200

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>200</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	17541573
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Alexis Swan
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	02-DEC-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	16:28:01
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$200
RAM confirmation Number	3729
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		17618CON6-Response-to-RR.pdf	84487 f308ac505e160e7c0136e2611028f9de0565946c	yes	2

**Multipart Description/PDF files in .zip description**

Document Description	Start	End
Response to Election / Restriction Filed	1	1
Applicant Arguments/Remarks Made in an Amendment	2	2

**Warnings:**

**Information:**

2	Fee Worksheet (SB06)	fee-info.pdf	30680 dcfa9166fb6a14c7122033ca134d777b200867ac	no	2
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**Warnings:**

**Information:**

**Total Files Size (in bytes):** 115167

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**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. 17618CON6 (AP)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Examiner: Marcela M Cordero Garcia

Serial No.: 13/961,828

Group Art Unit: 1658

Filed: August 7, 2013

Confirmation No. 9904

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Customer No.: 51957

**INTERVIEW SUMMARY, PRELIMINARY AMENDMENT, AND REMARKS**

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

Dear Sir:

Attached please find an interview summary, preliminary amendment to the claims, and accompanying remarks.

Amendments to the Claims begin at page 2;

Summary of the Interview begins at page 7;

Remarks follow on page 8.



**AMENDMENTS TO THE CLAIMS**

The following claims replace all prior versions of claims submitted in this application.

Only those claims being amended herein show their changes in highlighted form, where insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g. deletions or [[deletions]]).

1– 36. (Canceled)

37. (**Currently Amended**) A topical ophthalmic emulsion for treating an eye of a human having ~~KCS~~keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, ~~Penulen~~ acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is therapeutically effective in treating ~~KCS~~keratoconjunctivitis sicca.

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

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

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

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

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

Docket No. 17618CON6 (AP)

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

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

45. (**Currently Amended**) The topical ophthalmic emulsion of Claim 37, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight, ~~water,~~ and a buffer.

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

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

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

49. – 61. (Canceled)

62. (New) A topical ophthalmic emulsion for treating an eye of a human having dry eye, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.

Docket No. 17618CON6 (AP)

63. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

64. (New) The topical ophthalmic emulsion of Claim 63, wherein the tonicity agent or the demulcent component is glycerine.

65. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion further comprises a buffer.

66. (New) The topical ophthalmic emulsion of Claim 65, wherein the buffer is sodium hydroxide.

67. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

68. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

69. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

70. (New) The topical ophthalmic emulsion of Claim 62, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

71. (New) The topical ophthalmic emulsion of Claim 70, wherein the buffer is sodium hydroxide.

72. (New) The topical ophthalmic emulsion of Claim 62, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating dry eye, the blood of the human has substantially no detectable concentration of cyclosporin A.

73. (New) The topical ophthalmic emulsion of Claim 67, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

74. (New) A topical ophthalmic emulsion for increasing tear production in an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production in the eye of the human having keratoconjunctivitis sicca.

75. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

76. (New) The topical ophthalmic emulsion of Claim 75, wherein the tonicity agent or the demulcent component is glycerine.

77. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion further comprises a buffer.

78. (New) The topical ophthalmic emulsion of Claim 77, wherein the buffer is sodium hydroxide.

79. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

80. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

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81. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

82. (New) The topical ophthalmic emulsion of Claim 74, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

83. (New) The topical ophthalmic emulsion of Claim 82, wherein the buffer is sodium hydroxide.

84. (New) The topical ophthalmic emulsion of Claim 74, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in increasing tear production in the eye of the human having keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of cyclosporin A.

85. (New) The topical ophthalmic emulsion of Claim 79, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

## **SUMMARY OF INTERVIEW**

### Attendees, Date and Type of Interview

A telephone interview was conducted on December 4, 2013 and was attended by Examiner Cordero Garcia and Laura L. Wine.

### Identification of Claims Discussed

The Claims were discussed.

### Identification of References Discussed

U.S. Patent No. 5,474,979 to Ding et al. (“Ding”) and U.S. Application Serial No. 10/621,053 (published as U.S. Patent Application Publication No. 2005/0014691 and issued as US 6,984,628 to “Bakhit”) were discussed.

### Principal Arguments and Other Matters

The Applicants proposed presenting data and evidence to support the patentability of the pending claims in the form of declarations under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132.

### Results of Interview

It was agreed that the Applicants would submit data and evidence to support the patentability of the pending claims.

## REMARKS

Claim amendments and remarks are filed herewith in response to the December 4, 2013 interview. Claims 49-61 are newly cancelled. Claims 37, 44, 45, and 47 have been amended. Claims 62-85 are new. Thus, Claims 37-48 and 62-85 are currently pending. No new matter has been added by this amendment, and all amendments to the claims are fully supported by the originally filed application. The Applicants respectfully submit that the claims are in condition for allowance.

### Evidence of Unexpected Results

The Applicants submit that a *prima facie* case of obviousness cannot be properly established against the pending Claims in view of the prior art, such as the Ding reference. However, the Applicants submit that the unexpected results obtained with the claimed formulations overcome any *prima facie* obviousness rejection.

The Federal Circuit has held that objective evidence of nonobviousness must always be taken into account before a conclusion on obviousness is reached. Similarly, M.P.E.P. 716.01(a) states that “[a]ffidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-left but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the Patent Office in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103.” Thus, the *Graham* factors, including the use of objective evidence of secondary considerations to rebut a *prima facie* case of obviousness, remains the framework to be followed for a determination of obviousness. The Federal Circuit has even stated that “evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.” See, *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

#### *The Claimed Formulations Provide Surprising and Unexpected Results*

The claimed formulations provide surprising and unexpected results in view of the prior art (e.g. Ding). According to MPEP § 2144.05 (III), the Applicants can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing “(1)

[t]hat the prior art taught away from the claimed invention...or (2) **that there are new and unexpected results relative to the prior art.**” *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004).

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

As described by Dr. Schiffman and Dr. Attar in their respective declarations, supported by examples and experiments, the claimed formulations provided unexpected results compared to the prior art with regards to two key objective testing parameters for dry eye or keratoconjunctivis sicca: Schirmer Tear Testing and decrease in corneal staining, and with regards to reduction in blurred vision and decreased use of artificial tears. Specifically, the claimed formulations provided unexpected results compared to formulations 1E and 1D disclosed in Ding, which included 0.05% by weight cyclosporin A and 0.625% by weight castor oil and 0.10% by weight cyclosporin A and 1.25% by weight castor oil, respectively. *See* Ding, col. 4, lines 34-43.

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



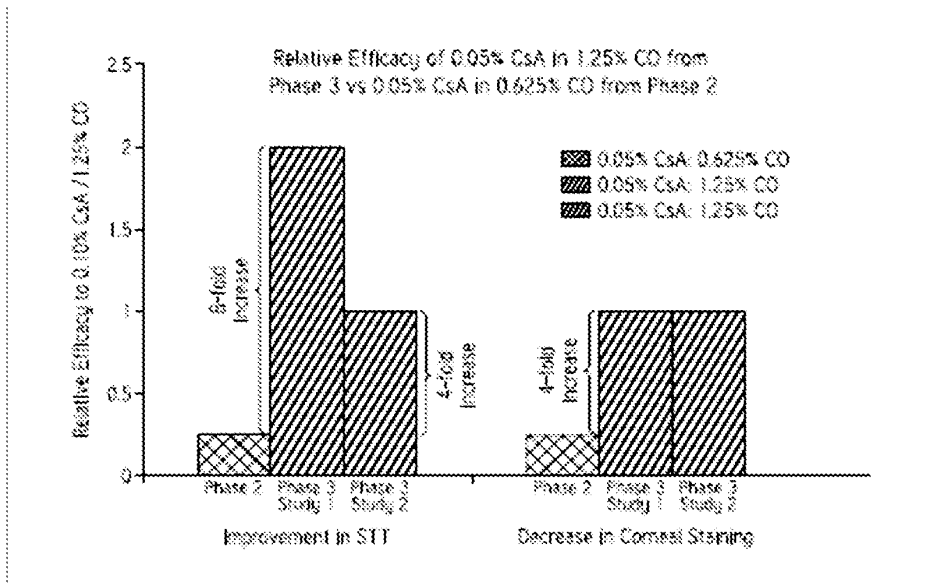
decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E). This was clearly a very surprising and unexpected result.

**Exhibit E of Schiffman Declaration 1**

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

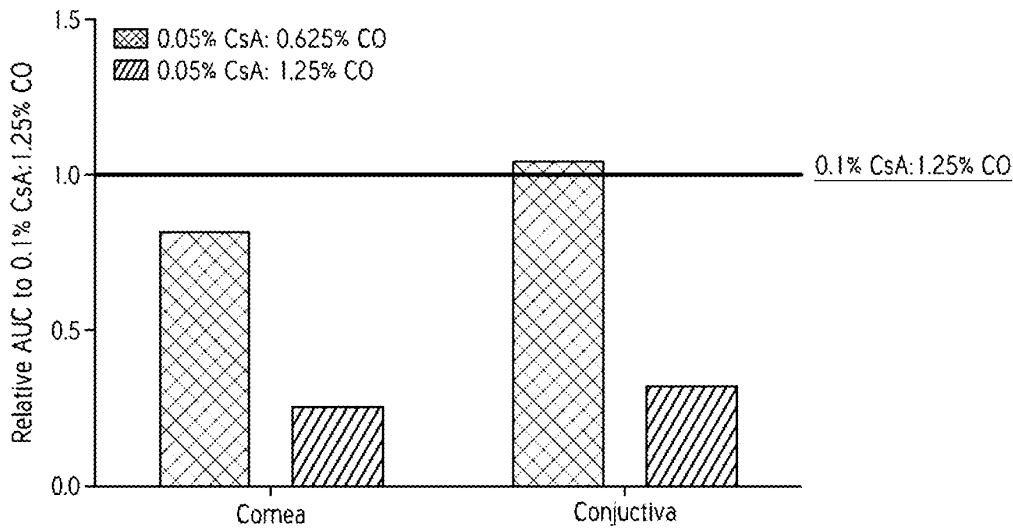
\*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

**Exhibit F of Schiffman Declaration 1**



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

**Exhibit B to Attar Declaration**



As described in paragraph 7 of the Attar Declaration, this chart shows that the amount of cyclosporin A that reaches the cornea and conjunctiva, ocular tissues that are highly relevant for the treatment of dry eye or keratoconjunctivitis sicca, is higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the claimed

formulation) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding 1D). According to Dr. Attar, this data teaches that the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil would be less therapeutically effective than the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil or the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil. Attar Declaration at ¶ 8. Similarly, according to Dr. Schiffman, this data shows that, since lower levels of cyclosporin A were reaching the ocular tissues relevant for the treatment of dry eye, one of skill in the art would have expected patients receiving the claimed formulation to exhibit a lesser decrease from baseline in corneal staining score and a lesser increase from baseline in Schirmer Score relative to the corneal staining scores and Schirmer Scores of the patients receiving the 0.05% by weight cyclosporin A / 0.625% by weight castor oil formulation (Ding 1E) in the Phase 2 trials, as illustrated in Schiffman Declaration 1, Exhibit B. *See* Schiffman Declaration 1 at ¶ 13.

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

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

Accordingly, the Applicants submit that the Declarations of Drs. Rhett M. Schiffman (Schiffman Declaration 1) and Attar, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed 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

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staining scores (key objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding, including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding 1D).

Hence, in view of the evidence presented above and presented in the attached declarations under 37 C.F.R. § 1.132, the Applicants submit that the unexpected results obtained from the claimed formulations successfully rebut any *prima facie* case of obviousness and support the patentability of the pending claims.

*35 U.S.C. § 102(e)*

The Examiner has brought the Bakhit reference to the Applicants' attention as a potential grounds for rejection of the pending Claims under 35 U.S.C. § 102(e). While the Applicants do not agree with the rejection, the Applicants submit that the claimed invention was reduced to practice before the effective date of the Bakhit reference (i.e. July 15, 2003), and thus the potential rejection under 35 U.S.C. § 102(e) is rendered moot. As evidence in support of this position, the Applicants submit herewith as Exhibit 3, a Declaration under 37 C.F.R. § 1.131 (hereinafter "131 Declaration") and associated exhibits.

Hence, in view of the evidence presented in the 131 Declaration and associated exhibits, the Applicants submit that the Claims were reduced to practice before the effective date of the Bakhit reference, and thus any rejection in view of the Bakhit reference is rendered moot.

**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.

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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 5, 2013

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

Please direct all inquiries and correspondence to:  
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2525 Dupont Drive, T2-7H  
Irvine, California 92612  
Tel: (714) 246-6996 Fax: (714) 246-4249

# EXHIBIT 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Dr. Rhett M. Schiffman,

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

1. I am currently a Vice President and Chief Medical Officer at Neurotech. I have an M.D, Masters Degrees in Clinical Research Design and Statistical Analysis and in Health Services Administration, a Bachelor's degree in Bioengineering, and over 12 years of experience in the pharmaceutical industry at Allergan, Inc. ("Allergan"). I was also a clinical investigator in the Phase 3 studies for Restasis®. I am a co-inventor on several issued patents and pending applications related to treatment methods using ophthalmic products. My *curriculum vita*, which contains a list of my publications to which I contributed, is attached to this declaration as Exhibit A.
2. I have been informed of the general nature of the rejections made by the Patent Office with respect to the previously presented claims of the above-referenced patent application and I am familiar with the references that the Patent Office has relied on in making these rejections. For example, I am aware of U.S. Patent No. 5,474,979 to Ding et al. ("Ding").
3. Restasis® is an FDA approved product that is a commercial embodiment of the invention. Specifically, Restasis® is approved as a 0.05% by weight cyclosporin ophthalmic emulsion useful for the treatment of ophthalmic conditions, such as dry eye. Specifically, Restasis® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
4. I have reviewed the pending claims in the present application, and the pending claims cover the specific formulation of Restasis® and/or the approved methods of treatment of dry eye or keratoconjunctivitis sicca for Restasis®.
5. In creating and testing the claimed methods and compositions, several unexpected benefits were discovered using the claimed compositions and/or claimed methods.
6. During development of a drug for the treatment of dry eye disease or keratoconjunctivitis sicca, Allergan performed a randomized, multicenter, double-masked, parallel-group, dose-response controlled Phase 2 trial on several cyclosporin-A and castor oil-containing formulations. In this Phase 2 study of moderate to severe KCS, the safety and efficacy of

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

7. As shown in Exhibit B, Figure 1, the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater decrease in corneal staining than the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation. As shown in Exhibit B, Figure 2 the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater increase in Schirmer Score (tear production) at week 12 than any other formulation tested, including the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation. Corneal staining and Schirmer score are key objective measures for determining dry eye or keratoconjunctivitis sicca disease severity.
8. After Allergan's Phase 2 study, Allergan initiated a Phase 3 study. In Allergan's multicenter, randomized, double-masked Phase 3 trials, Allergan compared the efficacy and safety of the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil to a the claimed formulation (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil), and to a vehicle containing 1.25% by weight castor oil. The data presented in Exhibit B represents the subpopulation of moderate to severe Phase 2 patients with the same reductions in tear production ( $\leq 5$  mm/5 min) as those enrolled in the Phase 3 studies. In this study, patients with moderate to severe dry eye disease were treated twice daily with either a formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil, a formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil, or the vehicle. Both cyclosporin A-containing formulations and the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate 80, 0.05% by weight Pemulen, sodium hydroxide, and water.



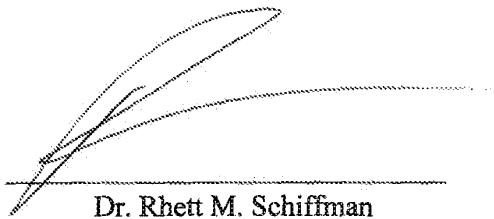
9. I have reviewed the Declaration of Dr. Mayssa Attar (“Attar Declaration”), and I agree with her statements made in paragraphs 6-8, reproduced here. I have attached Exhibit B to the Attar Declaration to this Declaration as Exhibit C:
10. “It was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A’s immunomodulatory properties to inhibit T cell activation which would lead to an increase in tear production and potentially other therapeutic effects related cyclosporine’s anti-inflammatory and anti-apoptotic effects and thus limit chronic inflammation in the pathology of dry eye. To elicit it’s therapeutic effect, cyclosporine must be effectively delivered to multiple target tissues of the ocular surface such as the cornea, conjunctiva, and lacrimal gland. The rate and extent at which cyclosporine is differentially delivered to the putative sites of action is critical to achieving therapeutic success in treating dry eye. Generally speaking, it was understood that pharmacokinetic/pharmacodynamic relationship would indicate that as more cyclosporin A reaches the target tissues of the ocular surface, such as the cornea and conjunctiva, the more immunomodulatory and more anti-inflammatory activity can take place and the more therapeutically effective a drug can be in treating dry eye.
11. Pharmacokinetic studies were performed on animal eyes, which compared the pharmacokinetic properties of several cyclosporin A-containing formulations. Those results are attached to this declaration in Exhibit B. As shown in Exhibit B, the relative extent at cyclosporin was absorbed increased in the relevant ocular tissues, here, the cornea and the conjunctiva, where the amount of oil present in the formulation was decreased. Specifically, the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil.
12. One of skill in the art would have understood such a result to mean that since there was more cyclosporin A present in the relevant ocular tissues in the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil and the formulation containing 0.1% by weight cyclosporine A and 1.25% by weight castor oil than the claimed formulation, that those formulations would have been more therapeutically effective than the claimed formulation. Specifically, this data suggests that the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil would have been more therapeutically effective than the claimed formulation.”

13. Specifically, one of skill in the art would have expected patients receiving the claimed formulations and methods to exhibit a lesser decrease from baseline in corneal staining score and a lesser increase from baseline in Schirmer Score, relative to the patient corneal staining scores and Schirmer Scores demonstrated by the patients receiving the 0.05% by weight cyclosporin A / 0.625% by weight castor oil formulation (Ding 1E) in the Phase 2 trials illustrated in Exhibit B.
14. Surprisingly, the claimed formulation and method was equally or more therapeutically effective for the treatment of dry eye/keratoconjunctivitis sicca than the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil according to at least four testing parameters. This result was surprising and completely unexpected. These results are attached to this declaration in Exhibit D.
15. As shown in the results in Exhibit D, the claimed formulation and method was unexpectedly superior to the 0.10% by weight cyclosporin A / 1.25% by weight castor oil formulation with respect to several properties. For example, the claimed formulations and methods surprisingly exhibited a comparable or greater decrease in corneal staining score (see Exhibit D, Figure 1), a greater increase in Schirmer Score (see Exhibit D, Figure 2), an improvement in the common dry eye/keratoconjunctivitis sicca symptom of blurred vision (see Exhibit D, Figure 3) and a greater decrease in the number of artificial tears used by patients (see Exhibit D, Figure 4) compared to the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil.
16. This result was even more surprising, given earlier testing from the Phase 2 study that illustrated that compositions containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil provided more improvement in objective measures (such as corneal staining and increase in Schirmer Score – as illustrated in Exhibit B) in dry eye patients than compositions containing 0.05% by weight cyclosporin A and 0.625% castor oil.
17. I have compared the objective results showing the surprising therapeutic efficacy of the claimed formulation and method relative to the 0.10% by weight cyclosporin A and 1.25% by weight castor oil formulation tested in Phase 3 to the 0.05% by weight cyclosporin A and 0.625% by weight castor oil formulation relative to the 0.10% by weight cyclosporin A and 1.25% by weight castor oil formulation tested in Phase 2. This comparison is attached to this declaration as Exhibit E.
18. As seen in Exhibit E, in the Phase 2 study, the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding 1E) only achieved 0.25 times the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor

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

19. As seen in Exhibit E, and further illustrated in Exhibit F, surprisingly, the claimed formulation and method demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test Score in the first study of phase 3 compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding Example 1E) in the Phase 2 study. Exhibits E and F also illustrate that the claimed formulations demonstrated a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation in the Phase 2 study, the formulation disclosed in the Ding reference (Ding 1E). This was clearly a very surprising result.
  
20. Taking the results of these studies together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly and unexpectedly critical for therapeutic effectiveness in the treatment of dry eye/keratoconjunctivitis sicca.

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



Dr. Rhett M. Schiffman

Date: 10/11/13

# EXHIBIT A

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

**Current Title:** Vice President and Chief Medical Officer  
Neurotech

**Work Address:** 900 Highland Corporate Drive  
Building #1, Suite #101  
Cumberland, RI 02864

**Home Address:** 1843 Temple Hills  
Laguna Beach, CA 92651

**Office Telephone:** (401) 495-2395  
**Cell Telephone:** (313) 516-6924  
**Email:** r.schiffman@neurotechusa.com

**EDUCATION:**

**Professional:** University of Michigan, School of Public Health,  
Ann Arbor, Michigan  
2000 M.H.S.A. Health Services Administration

University of Michigan, Rackham Graduate School,  
Ann Arbor, Michigan  
1989 M.S. Clinical Research Design & Statistical Analysis

Universidad Autonoma de Ciudad Juarez  
Instituto de Ciencias Biomedicas  
Juarez, Mexico  
1983 M.D. Medicine

**Undergraduate:** Columbia University  
School of Engineering and Applied Science  
New York, NY  
1978 B.S. Bioengineering

**POSTDOCTORAL TRAINING:**

**Fellow:** Uveitis and Ocular Immunology, National Eye Institute,  
National Institutes of Health, Bethesda, MD  
1996-1997

**Resident:** Ophthalmology, Henry Ford Hospital, Detroit, Michigan  
1993 - 1996

**Resident:** Internal Medicine, Henry Ford Hospital, Detroit, Michigan  
1984 - 1986

**Intern:** Internal Medicine, Henry Ford Hospital, Detroit, Michigan  
1983 - 1984

**CERTIFICATION AND LICENSURE**

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

**PROFESSIONAL SOCIETIES:**

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

**PROFESSIONAL EXPERIENCE:**

2013-Present Vice President and Chief Medical Officer, Neurotech

2010-2013 Board Member, Glaucoma Research Foundation

2009-2013 Ophthalmology Therapeutic Area Head

2008-2013 Head of Development for Emerging Markets

2007-2013 Head, Global Product Enhancement/Life Cycle Management

2005-2013 Vice President, Development for Ophthalmology and Botox, Allergan Pharmaceuticals

2003-Present Clinical Associate Professor and Attending Physician in Ophthalmology, University of California at Irvine.

2001-2005 Senior Director, Ophthalmology Clinical Research, Allergan Pharmaceuticals, Irvine, California

1999-2001 Member, Leadership Council, Eye Care Services, Henry Ford Health System, Detroit, MI

1999-2001 Director, Quality Improvement, Eye Care Services, Henry Ford Health System, Detroit, MI

1998-2001 Director of the African-American Initiative for Male Health Improvement (AIMHI). Eye Disease Screening Program in Southeast Michigan. Funded by the Michigan Department of Community Health.

1997-2001 Director of Uveitis Services, Eye Care Services, Henry Ford Health System, Detroit, MI  
Director of Clinical Research, Eye Care Services, Henry Ford Health System, Detroit, MI  
Staff Investigator, Center for Health Services Research, Henry Ford Health System, Detroit, MI

1996-2001 Reviewer to Special Study Section, National Eye Institute, National Institutes of Health, Bethesda, Maryland.

1999-2001 Director, Clinical Research, Eye Care Services, Henry Ford Hospital, Detroit, Michigan

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

**TEACHING EXPERIENCE:**

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

**BOOKS & MONOGRAPHS:**

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



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

**JOURNAL PUBLICATIONS:**

1. Day D.G., Walters T.R., Schwartz G.F., Mundorf T.K., Liu C., Schiffman R.M., Bejani M. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. *Br J Ophthalmol*. 2013 Jun 6. [Epub ahead of print]
2. Callanan DG, Gupta S, Boyer DS, Ciulla TA, Singer MA, Kuppermann BD, Liu CC, Li XY, Hollander DA, Schiffman RM, Whitcup SM; Ozurdex PLACID Study Group. Dexamethasone Intravitreal Implant in Combination with Laser Photocoagulation for the Treatment of Diffuse Diabetic Macular Edema. *Ophthalmology*. 2013 May 22. S0161-6420(13)00152-8.
3. Katz LJ, Rauchman SH, Cottingham AJ Jr, Simmons ST, Williams JM, Schiffman RM, Hollander DA. Fixed-combination brimonidine-timolol versus latanoprost in glaucoma and ocular hypertension: a 12-week, randomized, comparison study. *Curr Med Res Opin*. 2012 May;28(5):781-8
4. Katz, L.J., Rauchman, S.H., Cottingham Jr., A.J., Simmons, S.T., Williams, J.M., Schiffman, R.M., Hollander, D.A. Fixed-combination brimonidinetimolol versus latanoprost in glaucoma and ocular hypertension: A 12-week, randomized, comparison study. *Current Medical Research and Opinion* 28 (5) , pp. 781-788
5. Lowder, C., Belfort Jr., R., Lightman, S., Foster, C.S., Robinson, M.R., Schiffman, R.M., Li, X.-Y., Cui H, Whitcup, S.M. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol* 2011 129 (5):545-553
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7. Xu, K., McDermott, M., Villanueva, L., Schiffman, R.M., Hollander, D.A. Ex vivo corneal epithelial wound healing following exposure to ophthalmic nonsteroidal anti-inflammatory drugs. *Clin Ophthalmol* 2011 5 (1), pp. 269-274.
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9. Spaeth G, Bernstein P, Caprioli J, Schiffman RM. Control of Intraocular Pressure and Intraocular Pressure Fluctuation with Fixed Combination Brimonidine-Timolol versus Brimonidine or Timolol Monotherapy. *Am J Ophthalmol*. 2011 January;151:93-99.
10. Attar, M., Schiffman, R., Borbridge, L., Farnes, Q., Welty, D. Ocular pharmacokinetics of 0.45% ketorolac tromethamine. *Clin Ophthalmol* 2010 4(1), pp. 1403-1408
11. Craven, E.R., Liu, C.-C., Batoosingh, A., Schiffman, R.M., Whitcup, S.M. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. *Clin Ophthalmol* 2010 4 (1):1433-1440
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- Hollander, D.A. Methicillin resistance of Staphylococcus species among health care and nonhealth care workers undergoing cataract surgery. *Clin Ophthalmol.* 2010 4(1):1505-1514
13. Katz L, Cohen J, Batoosingh A, Felix C, Shu V, Schiffman R. Twelve-Month, Randomized Controlled Trial of the Efficacy and Safety of Bimatoprost 0.01%, 0.0125%, and 0.03% in Patients with Glaucoma or Ocular Hypertension. *Am J Ophthalmol.* 2010 April;149:661-671.
  14. Lewis R, Gross R, Sall K, Schiffman R, Liu C-C, Batoosingh A, (for the Ganfort® Investigators Group II ). The Safety and Efficacy of Bimatoprost/Timolol Fixed Combination: A 1-year Double-masked, Randomized Parallel Comparison to Its Individual Components in Patients With Glaucoma or Ocular Hypertension. *J Glaucoma.* 2010 August;19(6):424-426.
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29. Mangione CM, Lee PP, Spritzer K, Berry S, Hayes RD et. al: Development, Reliability, and Validity of the 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25). Accepted for publication in *Archives of Ophthalmology*.
30. Schiffman RM, Jacobsen G, Whitcup S: Visual Functioning and General Health Status in Patients with Uveitis. *Arch Ophthalmol* 2001 Jun;119(6):841-849.
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40. Gubbins G, Schiffman RM, Alipati R, Batra S.: Cocaine-Induced Hepatonephrotoxicity. *Henry Ford Hospital Medical Journal* 1990; 38:55-56.

**JOURNAL REVIEWER**

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

**SELECTED PAST SCIENTIFIC ACTIVITIES:**

HFHS Principal Investigator

1. Schiffman RM, Chew E, Ferris F, Ellwein L, Hays R, Mangione C: A Randomized Comparison of the Cost, Quality and Acceptability of Four Modes of Administration the National Eye Institute Visual Functioning Questionnaire-25. National Eye Institute.
2. Schiffman RM: National Eye Institute Refractive Error Correction Questionnaire (NEI-RECQ) Phase II Protocol. National Eye Institute through Emmes Corporation.
3. Schiffman RM, Lesser GL, Imami N, Trick GL: A 48-Month, Multi-Center, Randomized, Double-Masked, Placebo-Controlled, Clinical Study to Evaluate the Effectiveness and Safety of Oral Memantine in Daily Doses of 20 Mg and 10 Mg in Patients with Chronic Open-Angle Glaucoma at Risk for Glaucomatous Progression - Allergan Protocol 192944-005.
4. Schiffman RM: A Multicenter, Investigator-Masked, Randomized, Parallel-Group Study to Compare the Safety and Efficacy and Safety of Restasis™ (Cyclosporine 0.05% Ophthalmic Emulsion) vs. An Artificial Tear (Refresh®) Used Twice Daily for Three Months in Patients with Moderate to Severe Keratoconjunctivitis Sicca (Allergan Protocol 192371-008)
5. Schiffman RM, Patel S, Crosswell M and Shankle J: The Retinal Thickness Analyzer in the Management of Uveitic Cystoid Macular Edema.
6. Schiffman RM, Trick GL: Retinal Thickness Analyzer (RTA) - Clinical Validation Study. Talia Technology Ltd.
7. A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide Insert in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye. Bausch and Lomb.

**SCIENTIFIC ACTIVITIES:**

HFHS Collaborative Investigator:

1. Lesser B, Darnley D, Schiffman R: Ocular Hypertension Treatment Study. National Eye Institute, 1993- 1999.
2. Nussenblatt RB, Whitcup SM, Schiffman RM, et. al: The Treatment of Non-infectious Intermediate and Posterior Uveitis with Humanized Anti-Tac Monoclonal Antibody Therapy: Phase I and Phase II. National Eye Institute, National Institutes of Health.

# EXHIBIT B

Phase 2 Results - Phase 3 Target Subpopulation

Change from Baseline in Corneal Staining at Week 12

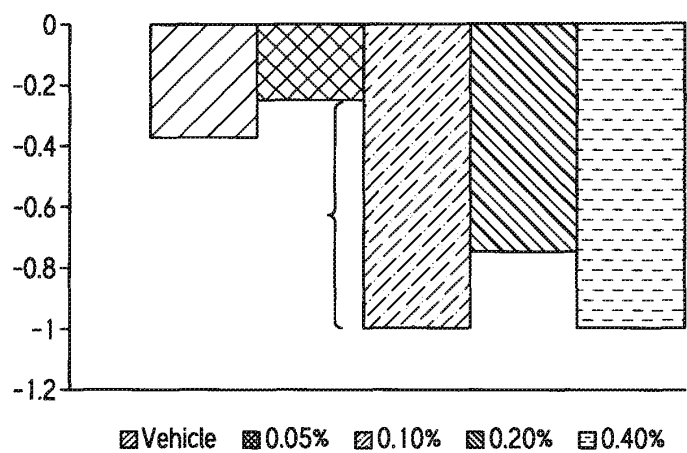


FIG. 1

Change from Baseline in Schirmer Score at Week 12

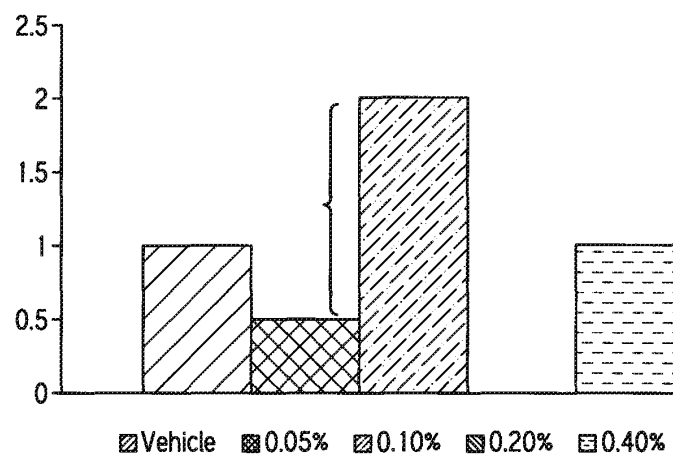
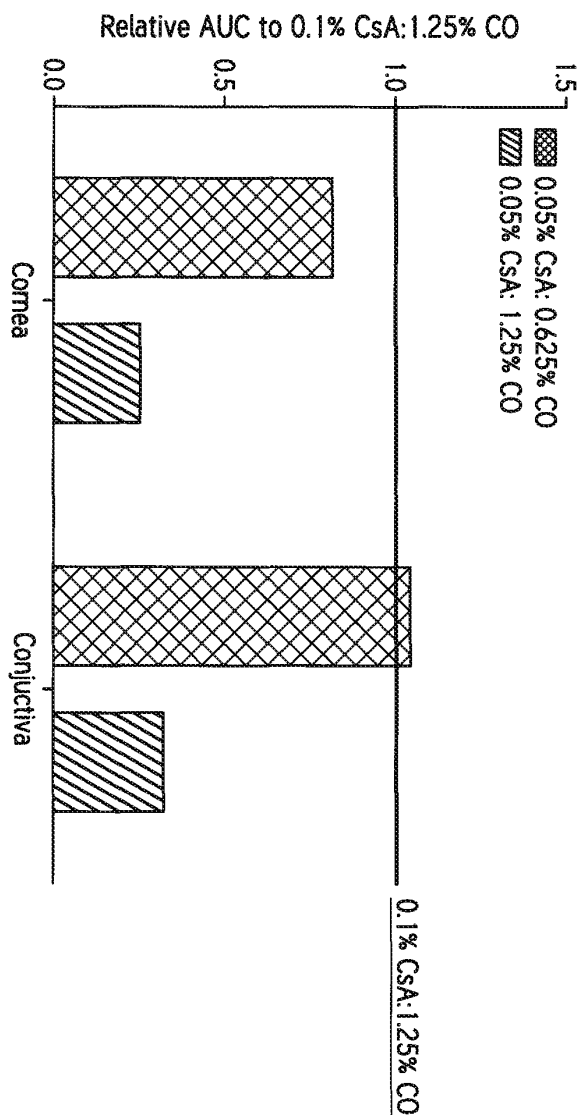


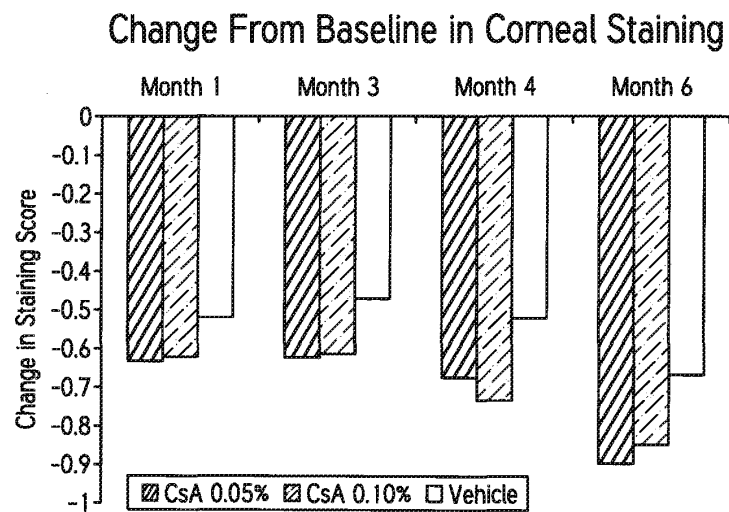
FIG. 2

# EXHIBIT C

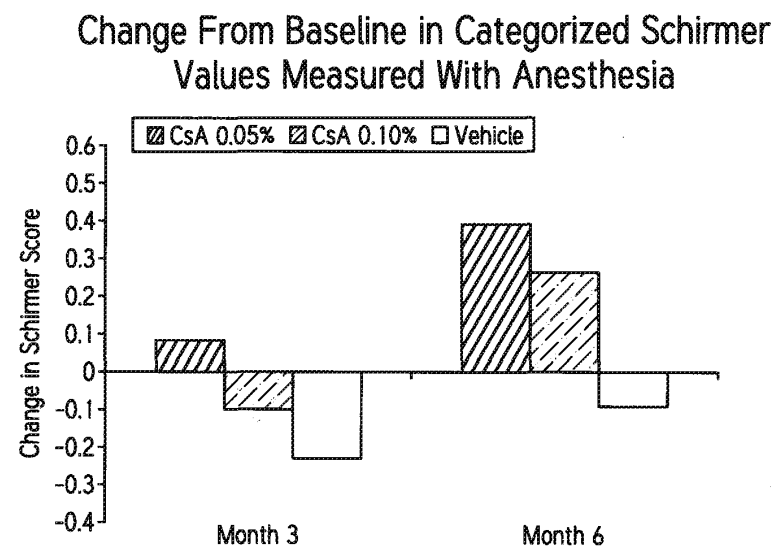




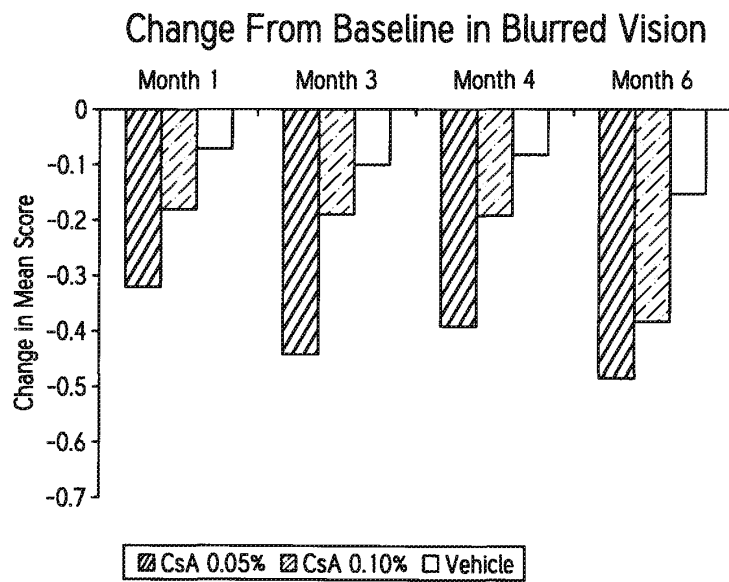
# EXHIBIT D



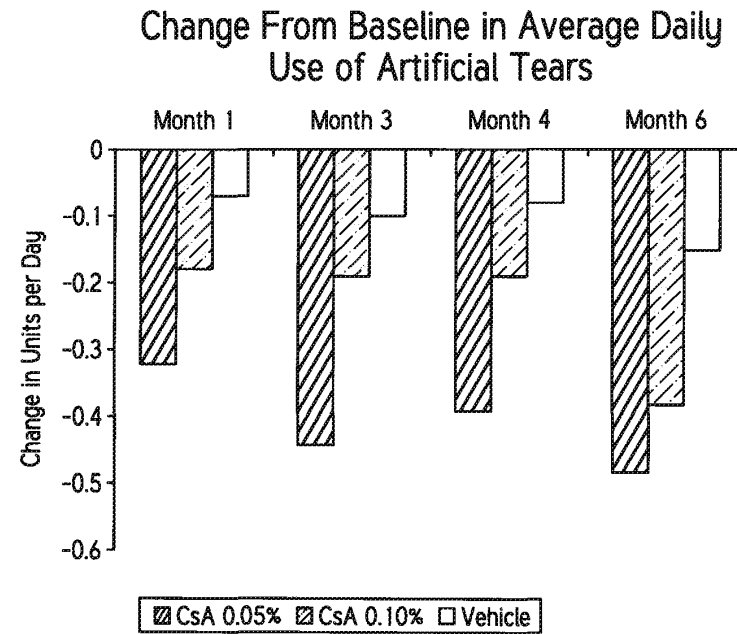
**FIG. 1**



**FIG. 2**



*FIG. 3*



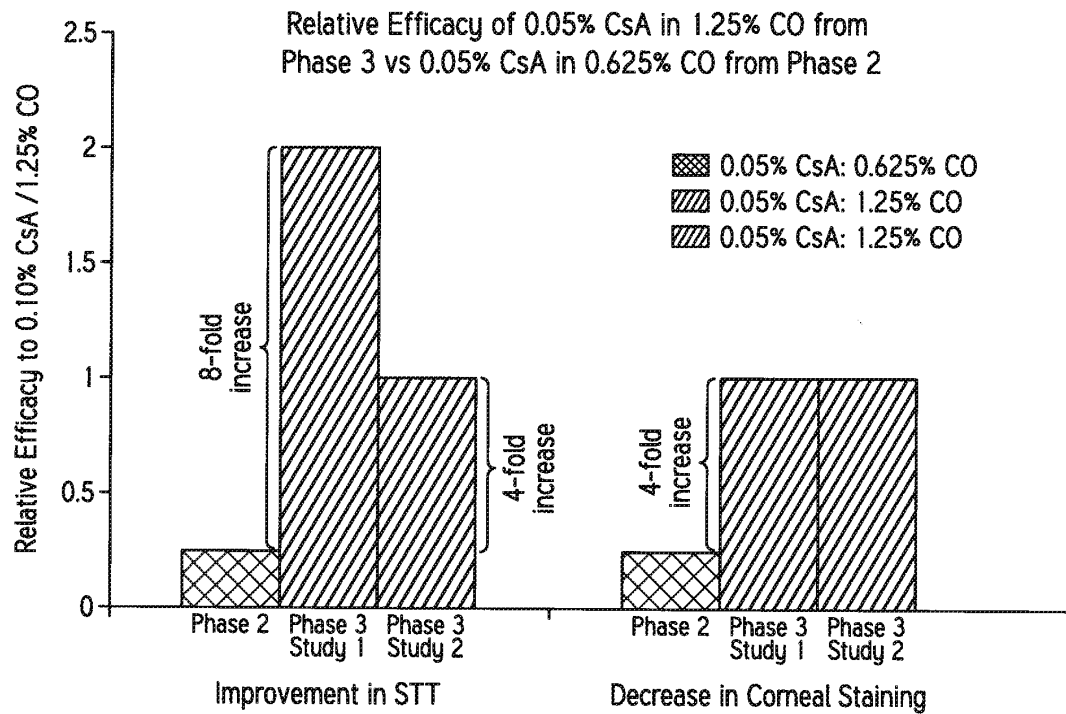
*FIG. 4*

# EXHIBIT E

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

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

# EXHIBIT F



## EXHIBIT 2



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132

of Dr. Mayssa Attar, Ph.D.

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

1. I am currently a Research Investigator at Allergan, Inc. ("Allergan"), specializing in preclinical and clinical pharmacokinetics and pharmacodynamics. I have a Ph.D. in Pharmaceutical Sciences, Bachelor's and Master's degrees in Biochemistry, and almost 15 years of experience in the pharmaceutical industry. I also serve as adjunct faculty at the the University of Southern California, School of Pharmacy. My *curriculum vita*, which contains a list of my publications to which I contributed, is attached to this declaration as Exhibit A.
2. I have been informed of the general nature of the rejections made by the Patent Office with respect to the previously presented claims of the above-referenced patent application and I am familiar with the references that the Patent Office has relied on in making these rejections. For example, I am aware of the "Ding" reference (U.S. Patent No. 5,474,979 to Ding et al.).
3. Restasis® is an FDA approved product that is a commercial embodiment of the invention. Specifically, Restasis® is approved as a 0.05% by weight cyclosporine ophthalmic emulsion useful for the treatment of ophthalmic conditions, such as dry eye. Specifically, Restasis® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
4. I have reviewed the pending claims in the present application, and the pending claims cover the specific formulation of Restasis® and/or the approved methods of treatment of dry eye or keratoconjunctivitis sicca with Restasis®.
5. In creating and testing the claimed methods and compositions, several unexpected results were discovered using the claimed compositions and methods.
6. It was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A's immunomodulatory properties to inhibit T cell activation, which would lead to an increase in tear production and potentially other therapeutic effects related to

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

7. Pharmacokinetic studies were performed on animal eyes, which compared the pharmacokinetic properties of several cyclosporin A-containing formulations. Those results are attached to this declaration in Exhibit B. As shown in Exhibit B, the relative extent that cyclosporin was absorbed increased in the relevant ocular tissues, here, the cornea and the conjunctiva, where the amount of oil present in the formulation was decreased but the weight percentage of cyclosporin stayed the same. Specifically, the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil, relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil. We also noticed that the amount of cyclosporin A that reached the relevant ocular tissue was higher for the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil than for the claimed formulation and method.
8. One of skill in the art would have understood such a result to mean that since there was more cyclosporin A present in the relevant ocular tissues with the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil and the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil than with the claimed formulation, that those formulations would have been more therapeutically effective than the claimed formulation. Specifically, this data teaches one of skill in the art that the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil would have been more therapeutically effective than the claimed formulation.
9. Surprisingly, an unexpected increase in efficacy was demonstrated relative to the 0.1% cyclosporin A and 1.25% castor oil formulation when we compared the therapeutic efficacy of the claimed formulation and method (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil) in our multicenter, randomized, double-masked Phase

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

10. As shown in Exhibits C and D, which are attached to this declaration, the corneal staining score and Schirmer scores were dramatically improved for the claimed methods (containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil) compared to the formulations disclosed in Example 1E in Ding (the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil).
11. I have read the Declaration of Dr. Rhett M. Schiffman, and I agree with his statements made at paragraphs 18-19. Exhibits E and F as referenced by Dr. Schiffman are attached as Exhibits C and D:
12. "As seen in Exhibit E, in the Phase 2 study, the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding 1E) only achieved 0.25 times the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation and only achieved 0.25 times the decrease in corneal staining as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation. However, in the Phase 3 studies, the claimed formulation and method achieved twice the improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the first study and substantially the same improvement in Schirmer Tear Test score as the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation in the second Phase 3 study. Also, the claimed formulation achieved substantially the same decrease in corneal staining score compared to the 0.1 % by weight cyclosporin A/1.25% by weight castor oil formulation.
13. As seen in Exhibit E, and further illustrated in Exhibit F, surprisingly, the claimed formulation and method demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test Score in the first study of phase 3 compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation (Ding Example 1E) in the Phase 2 study. Exhibits E and F also illustrate that the claimed formulations demonstrated a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation in the Phase 2 study, the formulation disclosed in the Ding reference (Ding 1E). This was clearly a very surprising result."
14. Taking the results of these studies together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical

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

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

A handwritten signature in black ink, consisting of several loops and a long horizontal stroke at the end, positioned above a solid horizontal line.

Mayssa Attar, Ph.D.

Date: 10-14-2013

# EXHIBIT A

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

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Linkedin Profile: <http://www.linkedin.com/pub/mayssa-attar/13/707/b90>

## PROFESSIONAL SUMMARY

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

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## PROFESSIONAL EXPERIENCE

### **ALLERGAN • Irvine, CA • 1/1999 – present**

#### **Research Investigator, Department of Pharmacokinetics and Drug Disposition**

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

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

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

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

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

**Research Associate, Hormones, Growth and Development Unit**

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

**EDUCATION**

**PhD, Pharmaceutical Sciences, University of Southern California, Los Angeles, CA**

Advisor: Vincent H L Lee, PhD, DSc

Thesis: Cytochrome P450 3A metabolism in the rabbit lacrimal gland and conjunctiva

**MSc, Biochemistry, University of Ottawa, Ottawa, ON**

Advisor: Nongnuj Tanphaichitr, PhD and Morris Kates, PhD

Thesis: A FTIR study of the interaction between sulfoglycolipid and phosphatidylcholine

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

**AWARDS AND HONORS**

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



## PROFESSIONAL AFFILIATIONS

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

## OTHER SKILLS

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

## PUBLICATIONS

### Articles and Book Chapters

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### **Abstracts and Posters**

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

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

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

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

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

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

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

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

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

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

## **Patents**

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

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

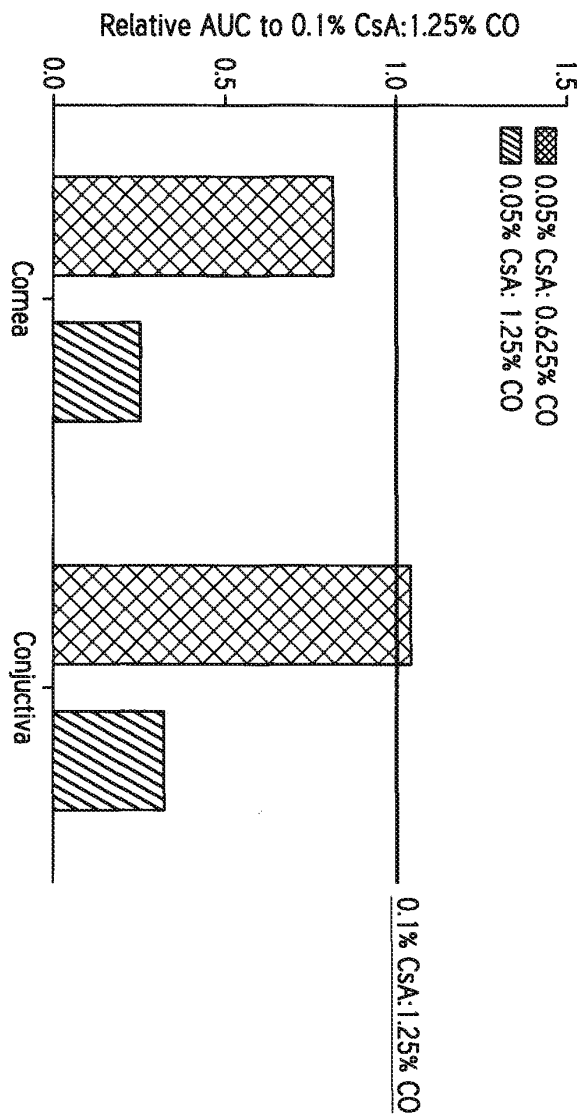
Morgan, A., Gore, A.V., Attar, M., Pujara, C. Cyclosporin emulsions. US Patent Application EP20110726545 Filed May 25, 2011. Patent Pending.

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

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

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

# EXHIBIT B



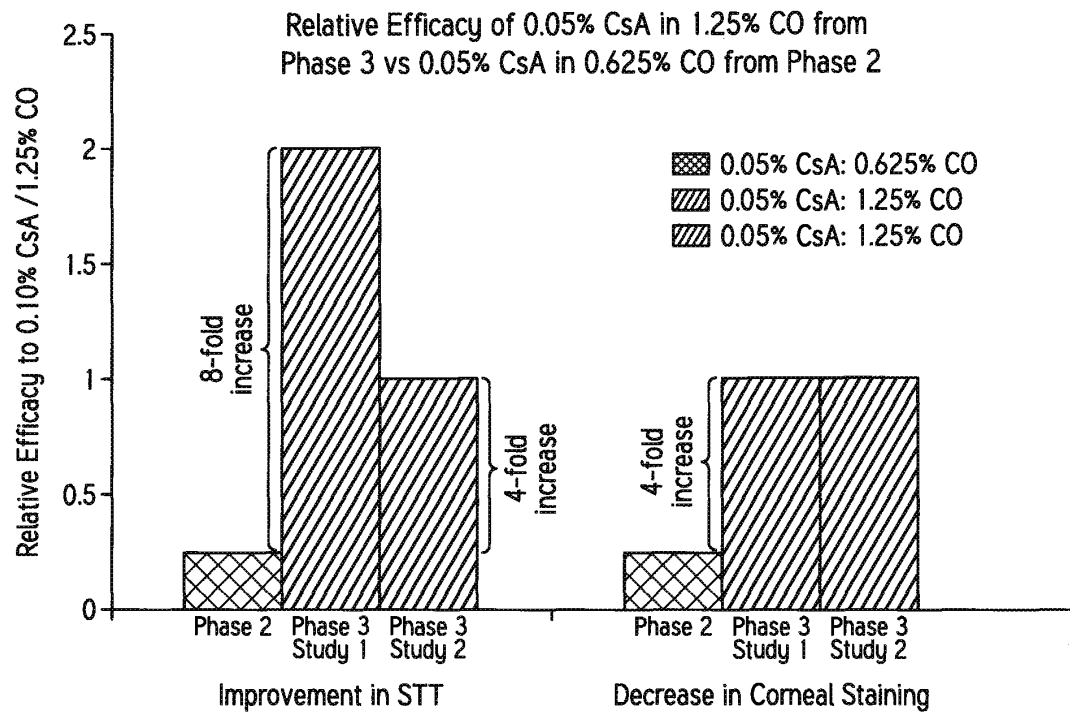
# EXHIBIT C

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

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



# EXHIBIT D



# EXHIBIT 3

Docket No. 17618CON6 (AP)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Examiner: Marcela M Cordero Garcia

Serial No.: 13/961,828

Group Art Unit: 1658

Filed: August 7, 2013

Confirmation No. 9904

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Customer No.: 51957

**DECLARATION PURSUANT TO 37 C.F.R. § 1.131**

Commissioner for Patents  
Alexandria, VA 22313-1450

We, Andrew Acheampong, Diane D. Tang-Liu, David F. Power, and Allergan, Inc., the assignee of the above-identified application and a party qualified under 37 C.F.R. § 1.46, having executed a Substitute Statement in lieu of Oath or Declaration under 35 USC § 115(d) and 37 CFR § 1.64 on behalf of James N. Chang, declare as follows:

1. We are the inventors of the above-described patent application or a party qualified under 37 C.F.R. § 1.46.
2. We have been advised that the Examiner has identified U.S. Patent Application Serial No. 10/621,053, published as U.S. Patent Application Publication No. 2005/0014691 and U.S. Patent No. 6,984,628 (“the ‘961 publication”) as a possible reference citable against the claims of the present application. We have been informed that the ‘961 publication has an effective filing date of July 15, 2003.
3. Prior to July 15, 2003, the invention as claimed in the above captioned U.S. Patent Application Ser. No. 13/961,828 was conceived and reduced to practice in the United

Docket No. 17618CON6 (AP)

States as evidenced by the documents attached hereto as Exhibit A and Exhibit B. Exhibit A includes pertinent portions of a Clinical Study Report for a Phase III study for RESTASIS® (the “clinical study report”) completed by Allergan, Inc. (“Allergan”), the assignee of record of the above captioned U.S. Patent Application, prior to July 15, 2003. Also, attached as Exhibit B is the pertinent portion of a formulation report for Allergan Formulation No. 9054X, referenced in the clinical study report. The dates on these documents have been redacted. The date of the Exhibits are both prior to July 15, 2003. Both Exhibits are confidential internal Allergan documents.

4. As shown on page 1 of Exhibit A, the clinical study report is on a multicenter, double-masked, randomized, vehicle-controlled, parallel-group study of the safety and efficacy of cyclosporine (ciclosporin) 0.05% and 0.1% ophthalmic emulsions in patients with moderate to severe keratoconjunctivitis sicca (or dry eye). Although the date has been redacted on this document, we confirm that the document is dated prior to July 15, 2003. Page 2 of Exhibit A shows another page of the clinical study report explaining that the investigational studies that were the subject of the clinical study report were conducted in the USA. Page 3 of Exhibit A shows another page of the clinical study report listing the investigational products for the study. On page 3, under IDENTITY OF INVESTIGATIONAL PRODUCTS, ciclosporin 0.05% ophthalmic emulsion is listed, with reference to Allergan formulation number 9054X. Exhibit B describes the formulation for Allergan formulation number 9054X which is an embodiment of the invention as claimed in the above-captioned U.S. Patent Application. As shown in Exhibit B, Allergan formulation number 9054X contains 0.05% cyclosporin A, 1.25% castor oil, 0.05% Pemulen TR-2 (an acrylate/C10-30 alkyl acrylate cross polymer), 2.2% glycerin, 1.0% polysorbate 80, water, and sodium hydroxide (a buffer) at a pH of 7.4. Although the date has been redacted on this document, we confirm that the document is dated prior to July 15, 2003.

5. Accordingly, the subject matter of the claimed invention was reduced to practice in the United States before the effective filing date of the ‘961 publication.

Docket No. 17618CON6 (AP)

I declare that the statements I have made in this declaration are true and that I made them knowing that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Date: 12/2/13

  
Andrew Acheampong

Docket No. 17618CON6 (AP)

I declare that the statements I have made in this declaration are true and that I made them knowing that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Date: Nov 30, 2013

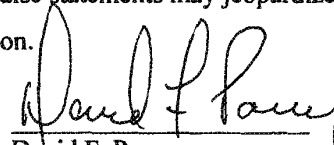
  
Diane D. Tang-Liu

43  
D.D.L.

Docket No. 17618CON6 (AP)

I declare that the statements I have made in this declaration are true and that I made them knowing that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Date: 11/29/2013

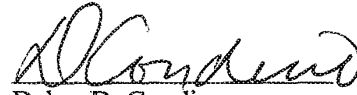
  
David F. Power



Docket No. 17618CON6 (AP)

I declare that the statements I have made in this declaration are true and that I made them knowing that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Date: 12/12/13



Debra D. Condino  
Assistant Secretary  
Allergan, Inc. (Assignee)

# EXHIBIT A

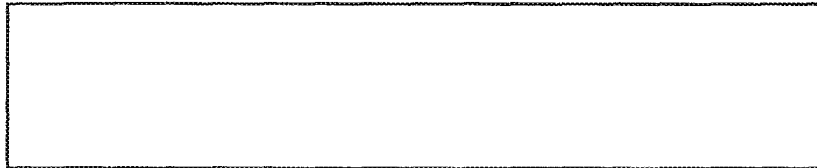
Allergan-Confidential

**CLINICAL STUDY REPORT**

**Study Title**

**A Multicentre, Double-Masked, Randomised, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Cyclosporine (Ciklosporin) 0.05% and 0.1% Ophthalmic Emulsions Used Twice Daily for Up To One Year in Patients with Moderate to Severe Keratoconjunctivitis Sicca**

**Study Number: 192371-002**

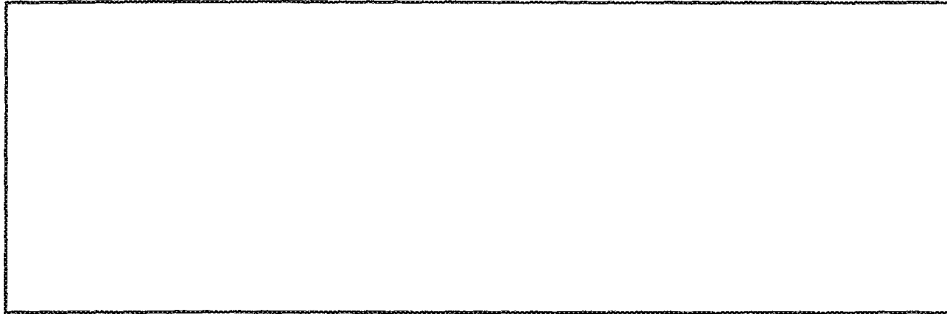


02NOV00 192371-002

**2. SYNOPSIS**

Name of Sponsor/Company: Allergan	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Ciclosporin	Volume:	
Name of Active ingredient: Ciclosporin	Page:	
<p><b>Title of study:</b> A multicentre, double-masked, randomised, vehicle-controlled, parallel-group study of the safety and efficacy of cyclosporine (ciclosporin) 0.05% and 0.1% ophthalmic emulsions used twice daily (BID) for up to one year in patients with moderate to severe keratoconjunctivitis sicca (KCS).</p> <p><b>Study Number:</b> 192371-002</p> <p><i>The clinical study report covers data collected from months 6 to 12, ie from end of vehicle-controlled masked treatment phase, to end of ciclosporin treatment extension phase.</i></p>		
<p><b>Study centre(s):</b> 14 investigational sites in the USA.</p>		

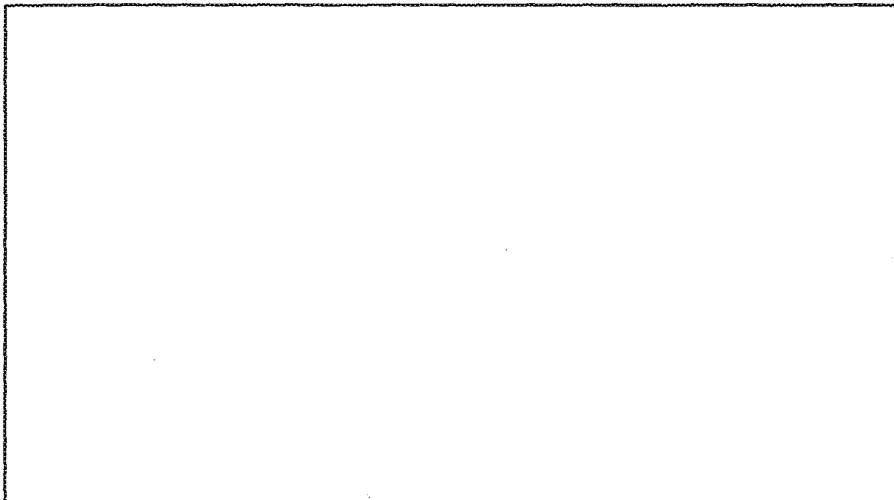
2



#### 9.4.2 IDENTITY OF INVESTIGATIONAL PRODUCT(S)

The investigational product (cyclosporin ophthalmic emulsion) was provided in unit dose vials. One vial contained one application for both eyes, and had the following identity:

- cyclosporin 0.05% ophthalmic emulsion (Allergan formulation number 9054X), which contained 0.05% cyclosporin, castor oil, glycerin, polysorbate 80, Pemulen, purified water, and sodium hydroxide to adjust pH to 7.4
- cyclosporin 0.1% ophthalmic emulsion (Allergan formulation number 8735X), which contained 0.10% cyclosporin, castor oil, glycerin, polysorbate 80, Pemulen, purified water, and sodium hydroxide to adjust pH to 7.4



3

# EXHIBIT B

### X-Number Formulation Report

X-Number: 09054X

Dosage Form: Emulsion

[1] SODIUM HYDROXIDE Grade: NF	7.4	pH	pH Adjust
GLYCERIN Grade: USP	2.2	% w/w	Other
CASTOR OIL Grade: USP	1.25	% w/w	Other
POLYSORBATE 80 Grade: NF	1.0	% w/w	Other
CYCLOSPORINE Grade: USP	0.05	% w/w	Active
[2] PEMULEN TR-2 Grade: NF	0.05	% w/w	Other
PURIFIED WATER Grade: USP	NA	% w/w	Competitor Ingd

[1]USE 5N SODIUM HYDROXIDE

[2]ACRYLIC ACID/ALKYL METHACRYLATE COPOLYMER BY BFGOODRICH

Page: 1

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	17582852
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Lauren Barberena
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	05-DEC-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	19:37:46
<b>Application Type:</b>	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	Applicant summary of interview with examiner	17618CON6_INTERVIEWSUMMARYANDRESPONSE.pdf	2823062 a1a2cbd09c8fc4e7387064981e6159b52c383fc4	no	72

### 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):**

2823062

**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.**

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.

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875			Application or Docket Number <b>13/961,828</b>	Filing Date <b>08/07/2013</b>	<input type="checkbox"/> To be Mailed
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO					
<b>APPLICATION AS FILED – PART I</b>					
(Column 1)			(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		
TOTAL CLAIMS (37 CFR 1.16(j))	minus 20 =	*	X \$ =		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =		
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		

<b>APPLICATION AS AMENDED – PART II</b>							
(Column 1)		(Column 2)		(Column 3)			
AMENDMENT	<b>12/05/2013</b>	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 36	Minus	** 25	= 11	X \$80 =	880
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$420 =	0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	<b>880</b>

(Column 1)		(Column 2)		(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))						
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE /ANTHONY WILLIAMS/	
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".							
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".							
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.							

This collection of information is required by 37 CFR 1.16. 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, 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.**  
 If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Document code: WFEE

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

Table with 4 columns: APPLICATION NUMBER (13/961,828), FILING OR 371(C) DATE (08/07/2013), FIRST NAMED APPLICANT (Andrew Acheampong), ATTY. DOCKET NO./TITLE (17618CON6 (AP))

CONFIRMATION NO. 9904

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

PUBLICATION NOTICE



Title:METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Publication No.US-2013-0338082-A1

Publication Date:12/19/2013

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 Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

<b>Doc Code: DIST.E.FILE</b> <b>Document Description: Electronic Terminal Disclaimer - Filed</b>		PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce
Electronic Petition Request	<b>TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION</b>	
Application Number	13961828	
Filing Date	07-Aug-2013	
First Named Inventor	Andrew Acheampong	
Attorney Docket Number	17618CON6 (AP)	
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	
<input checked="" type="checkbox"/> Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action  <input checked="" type="checkbox"/> This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.		
Owner	Percent Interest	
Allergan, Inc.	100%	
The owner(s) of 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 any patent granted on pending reference Application Number(s)		
12035698 filed on 02/22/2008 13649287 filed on 10/11/2012 13967168 filed on 08/14/2013 13967179 filed on 08/14/2013 13967189 filed on 08/14/2013 13967163 filed on 08/14/2013 11897177 filed on 08/28/2007		

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. 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 any patent granted on the reference application 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 any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: 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 shortened by any terminal disclaimer filed prior to its grant.

- 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

<b>Application Number:</b>	13961828			
<b>Filing Date:</b>	07-Aug-2013			
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong			
<b>Filer:</b>	Laura Lee Wine/Lauren Barberena			
<b>Attorney Docket Number:</b>	17618CON6 (AP)			
Filed as Large Entity				
<b>Utility under 35 USC 111(a) Filing Fees</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
Statutory or Terminal Disclaimer	1814	1	160	160
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>160</b>



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

Application No.: 13961828

Filing Date: 07-Aug-2013

Applicant/Patent under Reexamination: Acheampong et al.

Electronic Terminal Disclaimer filed on December 20, 2013

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

<b>EFS ID:</b>	17728432
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Lauren Barberena
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	20-DEC-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	15:51:25
<b>Application Type:</b>	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	5653
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 1.17 (Patent application and reexamination processing fees)
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<b>File Listing:</b>					
<b>Document Number</b>	<b>Document Description</b>	<b>File Name</b>	<b>File Size(Bytes)/ Message Digest</b>	<b>Multi Part /.zip</b>	<b>Pages (if appl.)</b>
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	38547	no	2
			70d9550e066f179e9c99a194d6340ac712f02975		
<b>Warnings:</b>					
<b>Information:</b>					
2	Fee Worksheet (SB06)	fee-info.pdf	30736	no	2
			5bb45a1145bc32c2853da8bcb051cafae313923		
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>			69283		
<p><b>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.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>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.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>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.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>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.</b></p>					



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 01/28/2014
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER

CORDERO GARCIA, MARCELA M

ART UNIT PAPER NUMBER

1676

DATE MAILED: 01/28/2014

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.

13/961,828 08/07/2013 Andrew Acheampong 17618CON6 (AP) 9904

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

Table with 7 columns: 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 04/28/2014

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

**PART B - FEE(S) TRANSMITTAL**

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

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

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

51957                      7590                      01/28/2014  
**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.
13/961,828	08/07/2013	Andrew Acheampong	17618CON6 (AP)	9904

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	04/28/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1676	514-020500

<p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. <b>Use of a Customer Number is required.</b></p>	<p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively, _____ 1</p> <p>(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. _____ 2</p> <p>_____ 3</p>
---	---

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

<p>4a. The following fee(s) are submitted:</p> <p><input type="checkbox"/> Issue Fee</p> <p><input type="checkbox"/> Publication Fee (No small entity discount permitted)</p> <p><input type="checkbox"/> Advance Order - # of Copies _____</p>	<p>4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)</p> <p><input type="checkbox"/> A check is enclosed.</p> <p><input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.</p> <p><input type="checkbox"/> 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).</p>
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5. **Change in Entity Status** (from status indicated above)

Applicant certifying micro entity status. See 37 CFR 1.29

Applicant asserting small entity status. See 37 CFR 1.27

Applicant changing to regular undiscounted fee status.

**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.

**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.

**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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

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

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
13/961,828 08/07/2013 Andrew Acheampong 17618CON6 (AP) 9904

51957 7590 01/28/2014
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER

CORDERO GARCIA, MARCELA M

ART UNIT PAPER NUMBER

1676

DATE MAILED: 01/28/2014

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

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

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

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

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

<b><i>Notice Requiring Inventor's Oath or Declaration</i></b>	Application No. 13/961,828	Applicant(s) Andrew Acheampong	
	Examiner CORDERO GARCIA, MARCELA M	Art Unit 1676	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) **MUST** be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

**INFORMAL ACTION PROBLEMS**

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Diane D. Tang-Liu**.

Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 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.



<b>Notice of Allowability</b>	<b>Application No.</b> 13/961,828	<b>Applicant(s)</b> ACHEAMPONG ET AL.	
	<b>Examiner</b> MARCELA M. CORDERO GARCIA	<b>Art Unit</b> 1676	<b>AIA (First Inventor to File) Status</b> 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 12/2/2013, 12/5/2013, 12/20/2013.  
 A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
2.  An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.
3.  The allowed claim(s) is/are 37-48 and 62-85. 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](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto: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)**

- |  |   |
|--|---|
| <ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</li> <li>2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br/>Paper No./Mail Date <u>9/5/2013, 9/25/2013</u></li> <li>3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material</li> <li>4. <input checked="" type="checkbox"/> Interview Summary (PTO-413),<br/>Paper No./Mail Date <u>20131220</u>.</li> </ol> | <ol style="list-style-type: none"> <li>5. <input checked="" type="checkbox"/> Examiner's Amendment/Comment</li> <li>6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance</li> <li>7. <input type="checkbox"/> Other _____.</li> </ol> |
|--|---|

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

### **DETAILED ACTION**

1. The present application is being examined under the pre-AIA first to invent provisions. This Office Action is in response to the replies received on 12/2/2013, 12/5/2013 and 12/20/2013.

#### ***Election/Restrictions***

2. Applicant's election without traverse of the species wherein the tonicity or demulcent component is "glycerin" and the buffer is "sodium hydroxide" in the reply filed on 12/02/2013 is acknowledged. Upon reconsideration, **the election of species mailed on 10/25/2013 is herein withdrawn** and all species are being examined.

#### ***Status of the claims***

3. Claims 37-61 were pending. Claim 49 was cancelled. Claims 62-85 are new claims. Claims 37 and 44 have been amended. Claims 37-48 and 62-85 are now pending. Claims 37-48 and 62-85 are presented for examination on the merits.

#### ***Declarations under 37 CFR 1.132***

4. The declaration under 37 CFR 1.132 by Rhett M. Schiffman filed on 12/5/2013 (EXHIBIT 1 comprising EXHIBITS A-F) is deemed sufficient to overcome a potential 103 rejection of claims 37-48 and 62-85 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/5/2013) 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) is deemed sufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/12/2013) as set forth in the last Office action because: EXHIBITS A-D were carefully reviewed. As described in paragraph 7 of the EXHIBIT 2, the chart in EXHIBIT B shows that the

amount of cyclosporin A that reaches the cornea and conjunctiva, ocular tissues that are highly relevant for the treatment of dry eye or keratoconjunctivitis sicca, is higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the claimed formulation) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D). According to Dr. Attar, this data teaches that the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil would be less therapeutically effective than the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil or the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil. EXHIBIT A, paragraph 8. Therefore it would be unexpected that the composition with lower uptake in cornea and conjunctiva would have significantly improved activity.

Taking the results of the studies and data presented in the EXHIBITS 1 and 2 together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca.

Accordingly, the Declarations in EXHIBIT 1 and EXHIBIT 2, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed formulations, including 0.05% by weight cyclosporin A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, including improved Schirmer Tear Test scores and corneal staining scores (key

objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding et al., including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D) which are the closest prior art formulations. The unexpected results are commensurate in scope with the claims (MPEP 716.02(d)).

Thus, a potential obviousness rejection in view of Ding et al. is rendered moot.

***Declaration under 37 CFR 1.131***

5. The 37 CFR 1.131 declaration filed on 12/5/2013 has been reviewed and accepted, thus obviating the need for a potential 102(e) rejection over US 6,984,628 (corresponding to US 2005/0014691, cited in the IDS dated 9/5/2013).

***Double Patenting***

6. A potential ODP rejection over Ding et al. (US 5,474,979, cited in the IDS dated 9/5/2013) is rendered moot for the reasons set forth in section 4 above.

***Terminal disclaimers***

7. Terminal disclaimers for 12/035,698; 13/649,287; 13/967,168; 13/967,179; 13/967,189; 13/967,163; 11/897,177 were received and accepted on 12/20/2013. Therefore, potential ODP rejections for these applications are rendered moot.

***Conclusion***

8. Claims 37-48 and 62-85 are allowed.

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

**REASONS FOR ALLOWANCE**

9. 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, cited in the IDS dated 9/5/2013), which would necessitate a potential 103 rejection and Bakhit et al. (US 6,984,628, corresponding to US 2005/0014691, cited in the IDS dated 9/5/2013) which would necessitate a potential 102(e) rejection. However, these potential rejections have been obviated in view of declarations under 1.132 and 1.131 as described in detail in paragraphs 4 and 5 above.

.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."

10. 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

Application/Control Number: 13/961,828  
Art Unit: 1676

Page 7

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 12/2013

<b>Applicant-Initiated Interview Summary</b>	<b>Application No.</b> 13/961,828	<b>Applicant(s)</b> ACHEAMPONG ET AL.	
	<b>Examiner</b> MARCELA M. CORDERO GARCIA	<b>Art Unit</b> 1676	

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

(1) MARCELA M. CORDERO GARCIA. (3)\_\_\_\_\_.

(2) LAURA L. WINE. (4)\_\_\_\_\_.

Date of Interview: 04 December 2013.

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

Exhibit shown or demonstration conducted:  Yes  No.  
If Yes, brief description: \_\_\_\_\_.

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

Claim(s) discussed: 37 and 44.

Identification of prior art discussed: Ding et al. (US 5,474,979, cited in the IDS dated 9/5/2013) and Bakhit et al. (US 6,984,628, corresponding to US 2005/0014691, cited in the IDS dated 9/5/2013).

**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 case and expedite any needed response. Examiner discussed potential rejections that would be needed with the closest prior art found (as set forth above). With respect to a potential 103 and ODP rejections over Ding et al. (See Examples, abstract and claims of Ding et al.), Applicant plans to file evidence of unexpected results. With respect to a potential 102(e) rejection over Bakhit et al. (US 6,928,628) (see Table 5 of Bakhit et al), Applicant's representative plans to file a 1.131 declaration. Upon careful consideration, no TD is deemed needed for Bakhit et al. In a telephonic conversation on 12/20/2013 Applicant's representative discussed the possibility of obviating the need of a TD for 11/897,177 wherein a previous restriction among product and method of using thereof had been made. Examiner noted that 35 USC 121 only applies to divisionals, not to continuations (See 92 USPQ2d 1289, Amgen Inc. v. F. Hoffmann-La Roche Ltd. U.S. Court of Appeals Federal Circuit Nos. 2009-1020, -1096. Decided September 15, 2009 580 F3d 1340). Therefore, a TD for 11/897,177 was still deemed necessary. TDs for 12/035,698; 13/649,287; 13/967,168; 13/967,179; 13/967,189; 13/967,163; 11/897,177 were requested by Examiner to obviate potential non-statutory DP rejections. Such TDs were received and approved on 12/20/2013.

<b>Notice of References Cited</b>	Application/Control No. 13/961,828	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO	Art Unit 1676	Page 1 of 1

**U.S. PATENT DOCUMENTS**

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A US-6,984,628	01-2006	Bakhit et al.	514/20.8
	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	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.


**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

**BIB DATA SHEET**
**CONFIRMATION NO. 9904**

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
13/961,828	08/07/2013	514	1676	17618CON6 (AP)		
<b>APPLICANTS</b> Allergan, Inc., Irvine, CA, Assignee (with 37 CFR 1.172 Interest); <b>INVENTORS</b> Andrew Acheampong, Irvine, CA; Diane D. Tang-Liu, Las Vegas, NV; James N. Chang, Newport Beach, CA; David F. Power, Hubert, NC; <b>** CONTINUING DATA *****</b> This application is a CON of 11/897,177 08/28/2007 PAT 8618064 and is a CON of 10/927,857 08/27/2004 ABN which claims benefit of 60/503,137 09/15/2003 <b>** FOREIGN APPLICATIONS *****</b> <b>** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **</b> 08/22/2013						
Foreign Priority claimed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	35 USC 119(a-d) conditions met <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<input type="checkbox"/> Met after Allowance	<b>STATE OR COUNTRY</b>	<b>SHEETS DRAWINGS</b>	<b>TOTAL CLAIMS</b>	<b>INDEPENDENT CLAIMS</b>
Verified and Acknowledged	/MARCELA M CORDEIRO GARCIA/ Examiner's Signature	Initials	CA	0	25	3
<b>ADDRESS</b> ALLERGAN, INC. 2525 DUPONT DRIVE, T2-7H IRVINE, CA 92612-1599 UNITED STATES						
<b>TITLE</b> METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS						
<b>FILING FEE RECEIVED</b> 3020	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		

Receipt date: 09/25/2013

13961828 - GAU: 1676

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828
	Filing Date	2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CON6-AP

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code <sup>1</sup>	Issue 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. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code <sup>1</sup>	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 <sup>3</sup>	Country Code <sup>2</sup>	Kind Code <sup>4</sup>	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T <sup>5</sup>
	1							<input type="checkbox"/>

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 <sup>5</sup>

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828	13961828 - GAU: 1676	
	Filing Date		2013-08-07		
	First Named Inventor		ACHEAMPONG, ANDREW		
	Art Unit		1653		
	Examiner Name		TBD		
	Attorney Docket Number		17618-US-CON6-AP		

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

1	U.S. Re-Examination Application: 90/009,944 and its entire prosecution history, Filed on August, 27, 2011 **	<input type="checkbox"/>
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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	12/20/2013
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\*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.

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

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-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).

\*\* Signature indicates consideration of publication and file history. The Examiner has access to these materials through the PTO computer systems. If additional copies are desired, please notify the Applicants through their attorneys.

- 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)	2013-09-25
Name/Print	Laura L. Wine	Registration Number	68,681

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


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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.

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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.
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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.



<b>Search Notes</b>  	<b>Application/Control No.</b>  13961828	<b>Applicant(s)/Patent Under Reexamination</b>  ACHEAMPONG ET AL.
	<b>Examiner</b>  MARCELA M CORDERO GARCIA	<b>Art Unit</b>  1676

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 38/13	12/27/2013	MMCG

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	12/27/2013	MMCG
STN search (attached)	12/27/2013	MMCG
also ran PALM Inventor search	12/27/2013	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST search	attached	12/27/2013	MMCG

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**EAST Search History****EAST Search History (Prior Art)**

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"13961828"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/12/27 11:30
L2	20	cyclosporin same castor same ("0.05") same ("1.25") AND ( (A61K38/13).CPC. )	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/12/27 11:32
L5	27	cyclosporin same castor same ("0.05") same ("1.25")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/12/27 11:37

**EAST Search History (Interference)**

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	3	cyclosporin same castor same ("0.05") same ("1.25") AND ( (A61K38/13).CPC. )	USPAT; UPAD	ADJ	ON	2013/12/27 11:36
L4	5	cyclosporin same castor same ("0.05") same ("1.25")	USPAT; UPAD	ADJ	ON	2013/12/27 11:36

12/ 27/ 2013 11:38:19 AM

C:\Users\mgarcia\Documents\EAST\Workspaces\1166940-b.wsp

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- NEWS 2 NOV 20 Get the Latest Version of STN Express, Version 8.5.2!
- NEWS 3 APR 29 Embase Alert (EMBAL) Enhanced with Articles-in-Press Content and Optimized for Use as a Companion Database for Embase
- NEWS 4 APR 30 Derwent WPI: The New Cooperative Patent Classification Is Now Available
- NEWS 5 MAY 21 STN Updated to Reflect Streamlining of CAS Roles
- NEWS 6 MAY 24 CABA Has Been Reloaded on May 24, 2013
- NEWS 7 MAY 28 STN Adds Indian Patent Full Text File - INFULL
- NEWS 8 JUL 09 TULSA and TULSA2 were reloaded on July 8, 2013
- NEWS 9 JUL 15 New IFIALL Database on STN Increases US Patent Retrieval Capabilities
- NEWS 10 JUL 24 Find the Most Comprehensive and Timely Results When Searching the Newly Enhanced Embase Alert(TM) together with Embase(TM)
- NEWS 11 JUL 31 New PV Cluster on STN(R) Simplifies Pharmacovigilance Alerting and Searching
- NEWS 12 AUG 15 PCTFULL documents with Chinese, Japanese, or Korean as filing language have English machine translations
- NEWS 13 AUG 16 The 2013 Inventory of Existing Chemical Substances in China is Now Available on STN
- NEWS 14 SEP 10 CAS Expands Coverage of Philippines Patents
- NEWS 15 SEP 13 STN on the Web Enhanced with Updated Structure and BLAST Plug-ins
- NEWS 16 SEP 24 Emtree Thesaurus Updated in Embase
- NEWS 17 SEP 27 Application Numbers for U.S. Patents in CA/CAplus and USPATFUL/USPAT2 Enhanced with U.S. Series Code Information
- NEWS 18 OCT 10 Additional Experimental Spectra Now Available
- NEWS 19 NOV 13 Removal of CHEMINFORMRX, DETHERM, CHEMSAFE and SPECINFO from STN
- NEWS 20 NOV 25 IFIALL Enhanced with the Addition of Cooperative Patent Classification (CPC) Data
  
- NEWS EXPRESS 20 NOV 2013 CURRENT WINDOWS VERSION IS V8.5.2, AND CURRENT DISCOVER FILE IS DATED 18 NOVEMBER 2013.
  
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PRIORITY APPLN. INFO.:

CN 2012-10011033

20120116

AB The ophthalmic emulsion gel is composed of hydrophilic polymer(polyalkenyl alc. or non-ionic surfactant emulsifier) 0.01-10, higher fatty acid glyceride(one or more of olive oil, peanut oil, castor oil, mineral oil, etc.) 0.01-10, hydrophobic drug cyclosporin A 0.001-10, gel matrix(one or more of hydroxypropyl Me cellulose, hydroxypropyl Et cellulose, Me cellulose, etc.) 0.02-10, pH regulator(one or more of NaOH, sodium bicarbonate, HCl, etc.) 0-10, osmotic pressure regulator(glucose, glycerol, 0.7-0.9% NaCl solution, mannitol or sorbitol) 0-10, and purified water 10-12 weight parts. The preparation method comprises mixing higher fatty acid glyceride with hydrophobic drug cyclosporin, dissolving, regulating pH to 3-9, obtaining oil phase; dissolving hydrophilic polymer in 1-2 parts of water for injection to obtain water phase; adding oil phase into water phase, mixing to obtain emulsion; adding 9-10 parts of water for injection into beaker, sprinkling gel matrix on the surface of water for injection, standing and swelling; mixing emulsion with gel, stirring, regulating pH with pH regulator to 3-9, adding osmotic pressure regulator till the osmotic pressure of mixed solution is 200-350 Osmol/kg, subpackaging, and sterilizing at 115-125 and 0.05-0.15 MPa for 15-25 min. The ophthalmic emulsion gel directly acts on infected part, and can throughly and effectively play its role.

L4 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2013 ACS on STN

ACCESSION NUMBER: 2008:739200 CAPLUS  
DOCUMENT NUMBER: 149:45292  
TITLE: Cyclosporin compositions  
INVENTOR(S): Graham, Richard S.; Tien, Walter L.; Attar, Mayssa; Schiffman, Rhett; Morgan, Aileen; Hollander, David A.  
PATENT ASSIGNEE(S): Allergan, Inc., USA  
SOURCE: U.S. Pat. Appl. Publ., 26 pp., Cont.-in-part of U.S. Ser. No. 781,095.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080146497	A1	20080619	US 2007-858200	20070920
US 20080039378	A1	20080214	US 2007-781095	20070720
US 20080207495	A1	20080828	US 2008-35698	20080222
AU 2008349774	A1	20090813	AU 2008-349774	20080918
CA 2700182	A1	20090813	CA 2008-2700182	20080918
WO 2009099467	A2	20090813	WO 2008-US76756	20080918
WO 2009099467	A3	20091022		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
EP 2190407	A2	20100602	EP 2008-872212	20080918
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS			

KR 2010091946	A	20100819	KR 2010-7008509	20080918
JP 2010540446	T	20101224	JP 2010-525937	20080918
IL 204614	A	20121129	IL 2008-204614	20080918
ZA 2009000448	A	20100526	ZA 2009-448	20090120
MX 2010003045	A	20100429	MX 2010-3045	20100319
IN 2010DN02414	A	20101001	IN 2010-DN2414	20100408
CN 101835463	A	20100915	CN 2008-80113223	20100426
AU 2013213743	A1	20130829	AU 2013-213743	20130809

PRIORITY APPLN. INFO.:

US 2006-60820239	P	20060725
US 2006-60829796	P	20061017
US 2006-60829808	P	20061017
US 2006-60869459	P	20061211
US 2007-60883525	P	20070105
US 2007-60916352	P	20070507
US 2007-781095	A2	20070720
AU 2007-276815	A3	20070723
US 2007-858200	A	20070920
WO 2008-US76756	W	20080918

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Disclosed herein are therapeutic methods, compns., and medicaments related to cyclosporine. Loss of corneal sensitivity is treated by administering a composition comprising cyclosporin A at a concentration of from about 0.0001 % (w/v) to less than about 0.05 % (w/v) to a person in need thereof. A composition containing cyclosporin A 0.05%, Pemulen TR-2 0.10%, Polysorbate 80 1.00%, glycerin 1.00%, mannitol 2.00%, NaOH to pH 7.35, and purified water q.s. to 100% gave the highest cyclosporin A ocular tissue exposure levels following a single ocular instillation.

L4 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2013 ACS on STN

ACCESSION NUMBER: 2006:590857 CAPLUS  
DOCUMENT NUMBER: 145:443655  
TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation  
AUTHOR(S): Yang, S. G.; Kim, D. D.; Chung, S. J.; Shim, C. K.  
CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul, S. Korea  
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (2006), 44(5), 233-239  
CODEN: ICTHEK; ISSN: 0946-1965  
PUBLISHER: Dustri-Verlag Dr. Karl Feistle  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved phys. stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to com. available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 Healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 mL of water with a

1-wk washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment C). Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concns. using a specific monoclonal RIA. Results: The differences in bioavailability parameters (i.e., AUC0-24h, AUC0-∞ and Cmax) between the treatments were within the range of 80 - 125% of the reference treatment. An anal. of variance (ANOVA) revealed no significant differences (p > 0.05) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and C) were also within the criteria. Conclusion: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the com. soft capsules of CsA using a volatile cosolvent such as ethanol.

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)  
 REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2013 ACS on STN  
 ACCESSION NUMBER: 2001:319777 CAPLUS  
 DOCUMENT NUMBER: 134:344591  
 TITLE: Method and compositions for administering taxanes orally to human patients  
 INVENTOR(S): Brodor, Samuel; Duchin, Kenneth; Selim, Sami  
 PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 45 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030448	A1	20010503	WO 2000-US29633	20001027
W:			AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW	
RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG	
CA 2389583	A1	20010503	CA 2000-2389583	20001027
EP 1225956	A1	20020731	EP 2000-972373	20001027
R:			AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL	
BR 2000015149	A	20021029	BR 2000-15149	20001027
HU 2002003303	A2	20030228	HU 2002-3303	20001027
HU 2002003303	A3	20050128		
JP 2003512443	T	20030402	JP 2001-532859	20001027
NO 2002002008	A	20020619	NO 2002-2008	20020426
MX 2002004164	A	20021017	MX 2002-4164	20020426
ZA 2002003358	A	20030429	ZA 2002-3358	20020426
IN 2002KN0545	A	20050923	IN 2002-KN545	20020426
PRIORITY APPLN. INFO.:			US 1999-60162310	P 19991027
			WO 2000-US29633	W 20001027

AB Taxane antineoplastic agents which exhibit poor or non-existent oral bioavailability are administered orally to human patients suffering from taxane-responsive disease conditions and made sufficiently bioavailable to achieve therapeutic blood levels. In a preferred embodiment, the taxane, preferably paclitaxel, is co-administered to the patient with an oral cyclosporin as bioavailability-enhancing agent, preferably cyclosporin A (CyA). The maximum effect of CyA on the enhancement of the exposure to paclitaxel was observed at a single dose of CyA of 15 mg/kg. By one preferred method, a dose of oral enhancer is administered about 0.5-72 h before the taxane and a second dose of the enhancer is administered immediately before, together with or immediately after the taxane. A method of treating human patients suffering from taxane-responsive disease conditions is also provided, as well as a method for providing such treatment while preventing or reducing hypersensitivity and allergic reactions without the need for premedication. For example, a male patient with prostate cancer received an enhancer (Sandimmune, 5 mg/kg in two doses, 1 h apart). Just after the 2nd dose, the patient drank a Cremophor EL/alc.-based solution of paclitaxel in a dose of 2 mg/kg. Plasma levels of 0.05  $\mu$ M of paclitaxel were present for about 10-12 h after oral administration of paclitaxel, i.e. levels comparable to those found in breast cancer patients receiving 96-h i.v. infusion of paclitaxel.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
 REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2013 ACS on STN  
 ACCESSION NUMBER: 1996:38846 CAPLUS  
 DOCUMENT NUMBER: 124:66660  
 ORIGINAL REFERENCE NO.: 124:12317a,12320a  
 TITLE: Lacrimal gland-specific emulsions for topical application to ocular tissue  
 INVENTOR(S): Ding, Shulin; Tien, Walter L.; Olejnik, Orest  
 PATENT ASSIGNEE(S): Allergan, Inc., USA  
 SOURCE: PCT Int. Appl., 27 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531211	A1	19951123	WO 1995-US6302	19950517
W:	AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ			
RW:	KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
US 5474979	A	19951212	US 1994-243279	19940517
CA 2190485	A1	19951123	CA 1995-2190485	19950517
CA 2190485	C	20030415		
CA 2309033	A1	19951123	CA 1995-2309033	19950517
CA 2309033	C	20030826		
AU 9526409	A	19951205	AU 1995-26409	19950517
AU 693213	B2	19980625		
EP 759773	A1	19970305	EP 1995-921294	19950517
EP 759773	B1	20010808		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE			
CN 1152876	A	19970625	CN 1995-194078	19950517



CN 1229136	C	20051130		
BR 9507664	A	19971007	BR 1995-7664	19950517
JP 10500414	T	19980113	JP 1995-529895	19950517
JP 3441462	B2	20030902		
EP 1044678	A1	20001018	EP 2000-202069	19950517
EP 1044678	B1	20030312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 203911	T	20010815	AT 1995-921294	19950517
ES 2161895	T3	20011216	ES 1995-921294	19950517
PT 759773	E	20020228	PT 1995-921294	19950517
AT 234076	T	20030315	AT 2000-202069	19950517
PT 1044678	E	20030829	PT 2000-202069	19950517
ES 2194670	T3	20031201	ES 2000-202069	19950517
MX 2002000724	A	20030425	MX 2002-724	19961115
CN 1288722	A	20010328	CN 2000-120126	20000714
CN 1198587	C	20050427		
HK 1034190	A1	20051209	HK 2001-104710	20010709
GR 3036945	T3	20020131	GR 2001-401814	20011018
KR 450703	B1	20041001	KR 2001-88637	20011229
JP 2003231646	A	20030819	JP 2003-63234	20030310
JP 4119284	B2	20080716		

PRIORITY APPLN. INFO.:

US 1994-243279	A	19940517
CA 1995-2190485	A3	19950517
EP 1995-921294	A3	19950517
JP 1995-529895	A3	19950517
WO 1995-US6302	W	19950517
KR 1996-706523	A3	19961118

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixt. with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporine A and the higher fatty acid glyceride may be castor oil. The composition allows a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues with enhanced absorption in the lacrimal gland. In addition, the composition has stability for up to 9 mo without crystallization of cyclosporin.

For example, an ophthalmic emulsion containing cyclosporin A 0.2, castor oil 2.5, Polysorbate-80 1.0, Pemulen 0.05, glycerol 2.2, NaOH q.s., and purified water to 100% was formulated to treat keratoconjunctivitis sicca.

OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 13 MEDLINE ® on STN  
 ACCESSION NUMBER: 2006296965 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 16724578  
 TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation.  
 AUTHOR: Yang S G; Kim D D; Chung S J; Shim C K  
 CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences and College of Pharmacy, Seoul National University, Seoul, Korea.  
 SOURCE: International journal of clinical pharmacology and therapeutics, (2006 May) Vol. 44, No. 5, pp. 233-9. Journal code: 9423309. ISSN: 0946-1965. L-ISSN: 0946-1965.  
 PUB. COUNTRY: Germany: Germany, Federal Republic of  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL) (CLINICAL TRIAL)

LANGUAGE: English  
FILE SEGMENT: MEDLINE; Priority Journals  
ENTRY MONTH: 200707  
ENTRY DATE: Entered STN: 27 May 2006  
Last Updated on STN: 12 Dec 2006  
Entered Medline: 20 Jul 2007

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

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

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

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

L4 ANSWER 7 OF 13 MEDLINE ® on STN  
ACCESSION NUMBER: 2000033859 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10564835  
TITLE: Pharmacokinetics and organ distribution of cyclosporin A incorporated in liposomes and mixed micelles.  
AUTHOR: Lee M K; Choi L; Kim M H; Kim C K  
CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Gu, Seoul, South Korea.  
SOURCE: International journal of pharmaceuticals, (1999 Nov 30) Vol. 191, No. 2, pp. 87-93.  
Journal code: 7804127. ISSN: 0378-5173. L-ISSN: 0378-5173.  
PUB. COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
LANGUAGE: English

FILE SEGMENT: MEDLINE; Priority Journals  
ENTRY MONTH: 200001  
ENTRY DATE: Entered STN: 24 Jan 2000  
Last Updated on STN: 24 Jan 2000  
Entered Medline: 11 Jan 2000

OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record  
AB The commercially available intravenous dosage form of cyclosporin A (C-CsA) contains a solubilizing agent, polyoxyethylated castor oil, which has been reported to be toxic. To replace the toxic solubilizing agent present in C-CsA, liposomal and mixed micellar preparations were made to solubilize CsA by the proliposome method and characterized. Furthermore, pharmacokinetics and organ distributions of these preparations were evaluated in comparison to C-CsA, which is micellar. The mean size of liposomal preparation (L-CsA) composed of DPPC/PA (molar ratio 3/1) and CsA was 43.6 nm and that of mixed micellar preparation (M-CsA) composed of DMPC/DSPE-PEG (molar ratio 95/5) and CsA was 6.5 nm. The solubilization of CsA was 2-fold greater in mixed micellar solution than in liposomes (0.06 vs 0.03 mg of CsA/mg of lipid). L-CsA, M-CsA and C-CsA were intravenously administered into rats via the femoral vein to analyze pharmacokinetics and organ distribution of CsA. M-CsA was not significantly different from C-CsA in every pharmacokinetic parameter studied. However, L-CsA resulted in 30% decrease in AUC and 55% increase in Cl(t) compared with C-CsA (P<0.05), without any significant differences in MRT, V(dss) and t(1/2). In addition, the distributions of M-CsA and L-CsA in different organs were not significantly different from those of C-CsA (0.05), except for a 51% decrease of M-CsA in the spleen at 4 h and a 33% increase of L-CsA in the liver at 4 h (P<0.05). These findings demonstrate that the liposomal preparation composed of DPPC/PA and CsA shows slightly different pharmacokinetics and organ distribution patterns from C-CsA, whereas the mixed micellar preparation composed of DMPC/DSPE-PEG and CsA exhibits similar patterns to C-CsA, as expected. Furthermore, these results suggest that those mixed micellar and liposomal preparations can replace C-CsA containing the toxic solubilizing agent, thus providing useful alternative dosage forms for intravenous administration of CsA.

L4 ANSWER 8 OF 13 MEDLINE ® on STN  
ACCESSION NUMBER: 1999238168 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10223652  
TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.  
AUTHOR: Acheampong A A; Shackleton M; Tang-Liu D D; Ding S; Stern M E; Decker R  
CORPORATE SOURCE: Allergan, Irvine, CA 92715, USA.  
acheampong\_andrew@Allergan.com  
SOURCE: Current eye research, (1999 Feb) Vol. 18, No. 2, pp. 91-103.  
Journal code: 8104312. ISSN: 0271-3683. L-ISSN: 0271-3683.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: MEDLINE; Priority Journals  
ENTRY MONTH: 199906  
ENTRY DATE: Entered STN: 14 Jun 1999  
Last Updated on STN: 14 Jun 1999  
Entered Medline: 2 Jun 1999

OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record  
AB PURPOSE: To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration.

METHODS: Radiolabeled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or

albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii) multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity.

RESULTS: After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (Cmax: dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (Cmax: dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (>300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-ciliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion.

CONCLUSIONS: Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

L4 ANSWER 9 OF 13 EMBASE COPYRIGHT (c) 2013 Elsevier B.V. All rights reserved on STN  
ACCESSION NUMBER: 2006216678 EMBASE  
TITLE: Stable bioavailability of cyclosporin A, regardless of food intake, from soft gelatin capsules containing a new self-nanoemulsifying formulation.  
AUTHOR: Yang, S.G.; Kim, D.D.; Chung, S.J.; Shim, C.-K., Dr. (correspondence)  
CORPORATE SOURCE: Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul 151-742, Korea, Republic of. shimck@snu.ac.kr  
AUTHOR: Shim, C.-K., Dr. (correspondence)  
CORPORATE SOURCE: Department of Pharmaceutics, College of Pharmacy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul 151-742, Korea, Republic of. shimck@snu.ac.kr  
SOURCE: International Journal of Clinical Pharmacology and Therapeutics, (May 2006) Vol. 44, No. 5, pp. 233-239.  
Refs: 22  
ISSN: 0946-1965 CODEN: ICTHEK  
COUNTRY: Germany  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 030 Clinical and Experimental Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered Embase: 30 May 2006  
Last Updated on Embase: 6 Sep 2007  
AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved physical stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to commercially available soft capsules containing CsA, in which

ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 ml of water with a 1-week washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment C). Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concentrations using a specific monoclonal radioimmunoassay. Results: The differences in bioavailability parameters (i.e., AUC<sub>0-24h</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub>) between the treatments were within the range of 80-125% of the reference treatment. An analysis of variance (ANOVA) revealed no significant differences (p > 0.05) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and C) were also within the criteria. Conclusion: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the commercial soft capsules of CsA using a volatile cosolvent such as ethanol. .COPYRG. 2006 Dustriverlag Dr. K. Feistle.

L4 ANSWER 10 OF 13 EMBASE COPYRIGHT (c) 2013 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999383199 EMBASE

TITLE: Pharmacokinetics and organ distribution of cyclosporin A incorporated in liposomes and mixed micelles.

AUTHOR: Lee, Mi-Kyung; Choi, Leena; Kim, Moon-Hee; Kim, Chong-Kook (correspondence)

CORPORATE SOURCE: Res. Inst. of Pharmaceutical Sci., Coll. Pharm., Seoul Natl. Univ., S., Seoul, Korea, Republic of. ckkim@plaza.snu.ac.kr

AUTHOR: Kim, Chong-Kook (correspondence)

CORPORATE SOURCE: Res. Institute Pharmaceutical Sci., College of Pharmacy, Seoul National University, San 56-1 Shinlim-Dong, Kwanak-Gu, Seoul 151-742, Korea, Republic of. ckkim@plaza.snu.ac.kr

SOURCE: International Journal of Pharmaceutics, (30 Nov 1999) Vol. 191, No. 2, pp. 87-93.  
Refs: 24  
ISSN: 0378-5173 CODEN: IJPHDE

PUBLISHER IDENT.: S 0378-5173(99)00260-4

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation  
030 Clinical and Experimental Pharmacology  
037 Drug Literature Index  
039 Pharmacy  
052 Toxicology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered Embase: 2 Dec 1999  
Last Updated on Embase: 2 Dec 1999

AB The commercially available intravenous dosage form of cyclosporin A (C-CsA) contains a solubilizing agent, polyoxyethylated castor oil,

which has been reported to be toxic. To replace the toxic solubilizing agent present in C-CsA, liposomal and mixed micellar preparations were made to solubilize CsA by the proliposome method and characterized. Furthermore, pharmacokinetics and organ distributions of these preparations were evaluated in comparison to C-CsA, which is micellar. The mean size of liposomal preparation (L-CsA) composed of DPPC/PA (molar ratio 3/1) and CsA was 43.6 nm and that of mixed micellar preparation (M-CsA) composed of DMPC/DSPE-PEG (molar ratio 95/5) and CsA was 6.5 nm. The solubilization of CsA was 2-fold greater in mixed micellar solution than in liposomes (0.06 vs 0.03 mg of CsA/mg of lipid). L-CsA, M-CsA and C-CsA were intravenously administered into rats via the femoral vein to analyze pharmacokinetics and organ distribution of CsA. M-CsA was not significantly different from C-CsA in every pharmacokinetic parameter studied. However, L-CsA resulted in 30% decrease in AUC and 55% increase in Cl(t) compared with C-CsA (P<0.05), without any significant differences in MRT, V(dss) and t(1/2). In addition, the distributions of M-CsA and L-CsA in different organs were not significantly different from those of C-CsA (P>0.05), except for a 51% decrease of M-CsA in the spleen at 4 h and a 33% increase of L-CsA in the liver at 4 h (P<0.05). These findings demonstrate that the liposomal preparation composed of DPPC/PA and CsA shows slightly different pharmacokinetics and organ distribution patterns from C-CsA, whereas the mixed micellar preparation composed of DMPC/DSPE-PEG and CsA exhibits similar patterns to C-CsA, as expected. Furthermore, these results suggest that those mixed micellar and liposomal preparations can replace C-CsA containing the toxic solubilizing agent, thus providing useful alternative dosage forms for intravenous administration of CsA. Copyright (C) 1999 Elsevier Science B.V.

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ACCESSION NUMBER: 1999105661 EMBASE

TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.

AUTHOR: Acheampong, Andrew A., Dr. (correspondence); Shackleton, Martha; Tang-Liu, Diane D.-S.; Ding, Shulin; Stern, Mike E.; Decker, Robert

CORPORATE SOURCE: Allergan, Irvine, CA, United States. acheampong\_andrew@Allergan.com

AUTHOR: Acheampong, Andrew A., Dr. (correspondence)

CORPORATE SOURCE: Allergan Inc., 2525 Dupont Drive, Irvine, CA 92715, United States. acheampong\_andrew@Allergan.com

SOURCE: Current Eye Research, (Feb 1999) Vol. 18, No. 2, pp. 91-103.  
Refs: 30  
ISSN: 0271-3683 CODEN: CEYRDM

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 012 Ophthalmology  
030 Clinical and Experimental Pharmacology  
037 Drug Literature Index  
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered Embase: 28 Apr 1999  
Last Updated on Embase: 28 Apr 1999

AB Purpose. To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration. Methods. Radiolabeled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii)

multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity. Results. After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (C(max): dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (C(max): dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (> 300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-ciliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion. Conclusions. Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

L4 ANSWER 12 OF 13 BIOSIS COPYRIGHT (c) 2013 The Thomson Corporation on STN

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

AB Aim: We recently succeeded in preparing soft gelatin capsules containing a new self-nanoemulsifying formulation consisting of cyclosporin A (CsA), triacetin, polyoxyl 40 hydrogenated castor oil, polysorbate 20, medium chain triglycerides and medium chain mono- and diglycerides. The soft capsules containing the new formulation exhibited a significantly improved physical stability in terms of the appearance of the gelatin capsule shells and the composition of the fill mass during long-term storage, compared to commercially available soft capsules containing CsA, in which ethanol was employed as a cosolvent of CsA. In the present study, the influence of a fat-rich meal on the bioavailability of CsA from the soft capsule containing the new formulation (test drug) was evaluated and the results compared to those obtained with a representative soft capsule of CsA. Volunteers and methods: A randomized, open-label, 3-way crossover study was performed in the test capsules and reference soft capsules, in a fasted state or after a fat-rich breakfast. 18 healthy male volunteers received a single dose of the reference formulation (Neoral, Novartis AG, Basel, Switzerland) or test formulation (2 capsules each, 200 mg as CsA) with 240 ml of water with a 1-week washout period between the treatments, after a fat-rich (670 kcal, 45 g fat) breakfast (for the test drug, Treatment A; for the reference drug, Treatment B) or a 12-h fasting (for the test drug, Treatment Q. Serial blood samples, collected over a 24-h period after the administration, were assayed for blood CsA concentrations using a specific monoclonal radioimmunoassay. Results: The differences in

bioavailability parameters (i.e., AUC(0-24h), AUC(0-infinity) and C-max) between the treatments were within the range of 80 - 125% of the reference treatment. An analysis of variance (ANOVA) revealed no significant differences ( $p > 0.05$ ) between subjects, formulations or periods. The 90% confidence intervals (CI) indicated that the differences between the treatments (Treatments A and B, Treatments A and Q) were also within the criteria. Conclusion: These results indicate that the bioavailability of CsA from the test drug is equivalent to reference in the fed state, and is likely to be less influenced by a fat-rich meal. Therefore, the new formulation of CsA using triacetin appears to have an advantage over the commercial soft capsules of CsA using a volatile cosolvent such as ethanol.

L4 ANSWER 13 OF 13 BIOSIS COPYRIGHT (c) 2013 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:68489 BIOSIS  
DOCUMENT NUMBER: PREV200000068489  
TITLE: Pharmacokinetics and organ distribution of cyclosporin A incorporated in liposomes and mixed micelles.  
AUTHOR(S): Lee, Mi-Kyung; Choi, Leena; Kim, Moon-Hee; Kim, Chong-Kook [Reprint author]  
CORPORATE SOURCE: College of Pharmacy, Research Institute of Pharmaceutical Sciences, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Gu, Seoul, 151-742, South Korea  
SOURCE: International Journal of Pharmaceutics (Amsterdam), (Nov. 30, 1999) Vol. 191, No. 2, pp. 87-93. print.  
CODEN: IJPHDE. ISSN: 0378-5173.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 9 Feb 2000  
Last Updated on STN: 3 Jan 2002

AB The commercially available intravenous dosage form of cyclosporin A (C-CsA) contains a solubilizing agent, polyoxyethylated castor oil, which has been reported to be toxic. To replace the toxic solubilizing agent present in C-CsA, liposomal and mixed micellar preparations were made to solubilize CsA by the proliposome method and characterized. Furthermore, pharmacokinetics and organ distributions of these preparations were evaluated in comparison to C-CsA, which is micellar. The mean size of liposomal preparation (L-CsA) composed of DPPC/PA (molar ratio 3/1) and CsA was 43.6 nm and that of mixed micellar preparation (M-CsA) composed of DMPC/DSPE-PEG (molar ratio 95/5) and CsA was 6.5 nm. The solubilization of CsA was 2-fold greater in mixed micellar solution than in liposomes (0.06 vs 0.03 mg of CsA/mg of lipid). L-CsA, M-CsA and C-CsA were intravenously administered into rats via the femoral vein to analyze pharmacokinetics and organ distribution of CsA. M-CsA was not significantly different from C-CsA in every pharmacokinetic parameter studied. However, L-CsA resulted in 30% decrease in AUC and 55% increase in  $Cl_t$  compared with C-CsA ( $P < 0.05$ ), without any significant differences in MRT,  $V_{dss}$  and  $t_{1/2}$ . In addition, the distributions of M-CsA and L-CsA in different organs were not significantly different from those of C-CsA ( $P > 0.05$ ), except for a 51% decrease of M-CsA in the spleen at 4 h and a 33% increase of L-CsA in the liver at 4 h ( $P < 0.05$ ). These findings demonstrate that the liposomal preparation composed of DPPC/PA and CsA shows slightly different pharmacokinetics and organ distribution patterns from C-CsA, whereas the mixed micellar preparation composed of DMPC/DSPE-PEG and CsA exhibits similar patterns to C-CsA, as expected. Furthermore, these results suggest that those mixed micellar and liposomal preparations can replace C-CsA containing the toxic solubilizing agent, thus providing useful alternative dosage forms for intravenous administration of CsA.



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COST IN U.S. DOLLARS                SINCE FILE      TOTAL
                                      ENTRY           SESSION
FULL ESTIMATED COST                89.62          89.86

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FILE CONTAINS CURRENT INFORMATION.  
 LAST RELOADED: Dec 13, 2013 (20131213/UP).

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FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 11:40:57 ON 27 DEC 2013
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L2          182 CYCLOSPORIN (10A) CASTOR
L3          0 CYCLOSPORIN (10A) CASTOR AND (0.05) (10A) (1.25)
L4          13 CYCLOSPORIN (10A) CASTOR AND (0.05)

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FILE 'STNGUIDE' ENTERED AT 11:42:35 ON 27 DEC 2013

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COST IN U.S. DOLLARS                SINCE FILE      TOTAL
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FULL ESTIMATED COST                1.17           91.03

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SESSION WILL BE HELD FOR 120 MINUTES  
 STN INTERNATIONAL SESSION SUSPENDED AT 11:50:23 ON 27 DEC 2013

Receipt date: 09/05/2013

13961828 - GAU: 1676

Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828
	Filing Date		2013-08-07
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

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

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code <sup>1</sup>	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3278447		1966-10-11	Thomas McNicholas	
	2	4388229		1983-06-14	Cherng-Chyi Fu	
	3	4388307		1983-06-14	Thomas Cavanak	
	4	4614736		1986-09-30	Delevallee et al	
	5	4649047		1987-03-10	Renee Kaswan	
	6	4764503		1988-08-16	Roland Wenger	
	7	4814323		1989-03-21	Andrieu et al	
	8	4839342		1989-06-13	Renee Kaswan	

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number		13961828	13961828 - GAU: 1676	
	Filing Date		2013-08-07		
	First Named Inventor		ACHEAMPONG, ANDREW		
	Art Unit		1653		
	Examiner Name		TBD		
	Attorney Docket Number		17618-US-CON6-AP		

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Receipt date: 09/05/2013	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07		
	First Named Inventor	ACHEAMPONG, ANDREW		
	Art Unit	1653		
	Examiner Name	TBD		
	Attorney Docket Number	17618-US-CON6-AP		

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

30	<a href="http://web.archive.org/web/2001030625323/http://www.surfactant.co.kr/surfactants/pegester.html">http://web.archive.org/web/2001030625323/http://www.surfactant.co.kr/surfactants/pegester.html</a> , 2001, 6 Pages, retrieved on 7/05/2008	<input type="checkbox"/>
31	HUNTER, P.A. ET AL, Cyclosporin A Applied Topically to the Recipient Eye Inhibits Corneal Graft Rejection, Clin Exp Immunol, 1981, 173-177, 45	<input type="checkbox"/>
32	JUMAA, MUHANNAD ET AL, Physicochemical Properties and Hemolytic Effect of Different Lipid Emulsion Formulations Using a Mixture of Emulsifiers, Pharmaceutica Acta Helvetiae, 1999, 293-301, 73	<input type="checkbox"/>
33	KANAI, A. ET AL, The Effect on the Cornea of Alpha Cyclodextrin Vehicle for Eye Drops, Transplantation Proceedings, Febraury 1989, 3150-3152, Vol. 21	<input type="checkbox"/>
34	KANPOLAT, AYFER ET AL, Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration, Cornea/External Disease, April 1994, 119-122, 20(2)	<input type="checkbox"/>
35	KAUR, RABINDER ET AL, Solid Dispersions of Drugs in Polyocethylene 40 Stearate: Dissolution Rates and Physico-Chemical Interactions, Journal of Pharmacy and Pharmacology, December 1979, 48P	<input type="checkbox"/>
36	KUWANO, MITSUAKI ET AL, Cyclosporine A Formulation Affects Its Ocular Distribution in Rabbits, Pharmaceutical Research, January 2002, 108-111, 19(1)	<input type="checkbox"/>
37	Lambert Technologies Corp. Material Safety Data Sheet for LUMULSE™ POE-40 MS KP, last revision 8/22/2003. 3 pages	<input type="checkbox"/>
38	LEIBOVITZ, Z. ET AL., Our Experience In Processing Maize (Corn) Germ Oil, Journal Of The American Oil Chemists Society, 02/1983, 395-399, 80 (2), US	<input type="checkbox"/>
39	LIXIN, XIE ET AL, Effect Of Cyclosporine A Delivery System in Corneal Transplantation, Chinese Medical Journal, 2002, 110-113, 115 (1), US	<input type="checkbox"/>
40	LOPATIN, D.E., Chemical Compositions and Functions of Saliva, 8/24/2001, 31 Pages	<input type="checkbox"/>

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

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

41	LYONS, R.T. ET AL, Influence of Three Emulsion Formulation Parameters on the Ocular Bioavailability of Cyclosporine A in Albino Rabbits, Am Assoc Pharm Sci, 2000, 1 Page, 2(4)	<input type="checkbox"/>
42	PEDERSEN, ANNE MARIE ET AL, Primary Sjogren's Syndrome: Oral Aspects on Pathogenesis, Diagnostic Criteria, Clinical Features and Approaches for Therapy, Expert Opin Pharma, 2001, 1415-1436, 2(9)	<input type="checkbox"/>
43	PHILLIPS, THOMAS ET AL, Cyclosporine Has a Direct Effect on the Differentiation of a Mucin-Secreting Cell Line, Journal of Cellular Physiology, 2000, 400-408, 184	<input type="checkbox"/>
44	PRESENT, D.H. ET AL, Cyclosporine and Other Immunosuppressive Agents: Current and Future Role in the Treatment of Inflammatory Bowel Disease, American Journal of Gastroenterology, 1993, 627-630, 88(5)	<input type="checkbox"/>
45	Restasis ® Product Information Sheet, Allergan, Inc., 2009, 5 Pages	<input type="checkbox"/>
46	Restasis® Increasing Tear Production, Retrieved on 08/14/2009, <a href="http://www.restasisprofessional.com/_clinical/clinical_increasing.htm">http://www.restasisprofessional.com/_clinical/clinical_increasing.htm</a> 3 pages	<input type="checkbox"/>
47	ROBINSON, N.A. ET AL, Desquamative Gingivitis: A Sign of Mucocutaneous Disorders - a Review, Australian Dental Journal, 2003, 205-211, 48(4)	<input type="checkbox"/>
48	RUDINGER, J., Characteristics of the Amino Acids as Components of a Peptide Hormone Sequence, Peptide Hormones, 1976, 1-7	<input type="checkbox"/>
49	SALL, KENNETH ET AL, Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, Ophthalmology, 2000, 631-639, 107	<input type="checkbox"/>
50	SANDBORN, WILLIAM ET AL, A Placebo-Controlled Trial of Cyclosporine Enemas for Mildly to Moderately Active Left-Sided Ulcerative Colitis, Gastroenterology, 1994, 1429-1435, 106	<input type="checkbox"/>
51	SANDBORN, WILLIAM ET AL, Cyclosporine Enemas for Treatment-Resistant, Mildly to Moderately Active, Left-Sided Ulcerative Colitis, American Journal of Gastroenterology, 1993, 640-645, 88(5)	<input type="checkbox"/>

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

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

52	SCHWAB, MATTHIAS ET AL, Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel Disease, Clin Pharm, 2001, 723-751, 60(10)	<input type="checkbox"/>
53	SECCHI, ANTONIO ET AL, Topical Use of Cyclosporine in the Treatment of Vernal Keratoconjunctivitis, American Journal of Ophthalmology, December 1990, 641-645, 110	<input type="checkbox"/>
54	SMALL, DAVE ET AL, The Ocular Pharmacokinetics of Cyclosporine in Albino Rabbits and Beagle Dogs, Ocular Drug Delivery and Metabolism, 1999, 54	<input type="checkbox"/>
55	SMALL, DAVID ET AL, Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease, Journal of Ocular Pharmacology and Therapeutics, 2002, 411-418, 18(5)	<input type="checkbox"/>
56	SMILEK, DAWN ET AL, A Single Amino Acid Change in a Myelin Basic Protein Peptide Confers the Capacity to Prevent Rather Than Induce Experimental Autoimmune Encephalomyelitis, Proc. Natl. Acad. Sci., Nov 1991, 9633-9637, 88	<input type="checkbox"/>
57	STEPHENSON, MICHELLE, The Latest Uses Of Restasis, Review Of Ophthalmology, 12/30/2005, 7 Pages, US	<input type="checkbox"/>
58	STEVENSON, DARA ET AL, Efficacy and Safety of Cyclosporin A ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease, Ophthalmology, 2000, 967-974, 107	<input type="checkbox"/>
59	TESAVIBUL, N. ET AL, Topical Cyclosporine A (CsA) for Ocular Surface Abnormalities in Graft Versus Host Disease Patients, Invest Ophthalmol Vis Sci, Feb 1996, S1026, 37(3)	<input type="checkbox"/>
60	The Online Medical Dictionary, Derivative, Analog, Analogue, Xerostomia, accessed 7/7/2005 and 7/13/2005, 6 Pages	<input type="checkbox"/>
61	TIBELL, A. ET AL., Cyclosporin A In Fat Emulsion Carriers: Experimental Studies On Pharmacokinetics And Tissue Distribution, Pharmacology & Toxicology, 1995, 115-121, 76, US	<input type="checkbox"/>
62	TSUBOTA, KAZUO ET AL, Use of Topical Cyclosporin A in a Primary Sjogren's Syndrome Mouse Model, Invest Ophthalmol Vis Sci, Aug. 1998, 1551-1559, 39(9)	<input type="checkbox"/>

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

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

63	VAN DER REIJDEN, WILLY ET AL, Treatment of Oral Dryness Related Complaints (Xerostomia) in Sjogren's Syndrome, Ann Rheum Dis, 1999, 465-473, 58	<input type="checkbox"/>
64	WINTER, T.A. ET AL, Cyclosporin A Retention Enemas in Refractory Distal Ulcerative Colitis and 'Pouchitis', Scand J Gastroenterol, 1993, 701-704, 28	<input type="checkbox"/>
65	U.S. Pending Application: 13/967,189 Filed on August 14, 2013	<input type="checkbox"/>
66	U.S. Pending Application: 13/976,179 Filed on August 14, 2013	<input type="checkbox"/>
67	U.S. Pending Application: 13/961,818 Filed on August 07, 2013	<input type="checkbox"/>
68	U.S. Pending Application: 13/961,835 Filed on August 07, 2013	<input type="checkbox"/>
69	U.S. Pending Application: 13/961,808 Filed on August 07, 2013	<input type="checkbox"/>
70	U.S. Pending Application: 13/967,163 Filed on August 14, 2013	<input type="checkbox"/>
71	U.S. Pending Application: 13/967,168 Filed on August 14, 2013	<input type="checkbox"/>

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	12/20/2013
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\*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.

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-AP	

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

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> ( Not for submission under 37 CFR 1.99)	Application Number	13961828	13961828 - GAU: 1676
	Filing Date	2013-08-07	
	First Named Inventor	ACHEAMPONG, ANDREW	
	Art Unit	1653	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CON6-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).

\*\* Signature indicates consideration of publication and file history. The Examiner has access to these materials through the PTO computer systems. If additional copies are desired, please notify the Applicants through their attorneys.

- 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)	2013-09-04
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 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.



<b>Issue Classification</b> 	<b>Application/Control No.</b> 13961828	<b>Applicant(s)/Patent Under Reexamination</b> ACHEAMPONG ET AL.
	<b>Examiner</b> MARCELA M CORDERO GARCIA	<b>Art Unit</b> 1676

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION														
CLASS			SUBCLASS			CLAIMED					NON-CLAIMED									
514			20.5			A	6	1	K	38 / 13 (2006.01.01)										
<b>CROSS REFERENCE(S)</b>																				
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)																			

NONE		<b>Total Claims Allowed:</b>	
(Assistant Examiner)	(Date)	36	
/MARCELA M CORDERO GARCIA/ Primary Examiner. Art Unit 1676	12/27/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none



Docket No. 17618CON6 (AP)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Serial No.: 13/961,828

Filed: August 7, 2013

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Examiner: Marcela M. Cordero Garcia

Group Art Unit: 1676

Confirmation No. 9904

Customer No.: 51957

**RESPONSE TO NOTICE REQUIRING INVENTOR'S OATH OR DECLARATION**

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

Dear Sir:

The Applicants were informed via a telephone conversation with the USPTO on January 28, 2014 that the Notice Requiring Inventor's Oath or Declaration mailed January 28, 2014 in the above-referenced case was issued in error and would be withdrawn (confirmation no. 1-291829040).

Nevertheless, in order to expedite issuance of the above-referenced application, in response to the Notice Requiring Inventor's Oath or Declaration, Applicants respectfully submit herewith as EXHIBIT A a copy of Inventor Diane D. Tang-Liu's Declaration, which was properly executed under 37 C.F.R. 1.63 or 1.64 and filed with the USPTO via EFS on October 8, 2013. A copy of the electronic acknowledgement receipt for the Declaration in the above-referenced application is also attached for your reference as EXHIBIT B. If any questions remain, the Office is encouraged to contact the undersigned at (714)246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: January 28, 2014

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

Docket No. 17618CON6 (AP)

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

# EXHIBIT A

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.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**

<b>Title of Invention</b>	<b>METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS</b>
---------------------------	--

As the below named inventor, I hereby declare that:

This declaration is directed to:  The attached application, or  
 United States application or PCT international application number \_\_\_\_\_  
filed on \_\_\_\_\_.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

**LEGAL NAME OF INVENTOR**

Inventor: Diane D. Tang-Liu Date (Optional) : \_\_\_\_\_  
Signature: *Diane Tang-Liu*

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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.

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



# EXHIBIT B

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	17067912
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Alexis Swan
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	08-OCT-2013
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	13:36:48
<b>Application Type:</b>	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	Oath or Declaration filed	17618-Tang-Liu-Declaration.pdf	115996 e6cccf12c8997e0cd437abb948b1271c3c3b1e2	no	1

### Warnings:

### Information:

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

<b>EFS ID:</b>	18049061
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Maria Stein
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	28-JAN-2014
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	16:24:16
<b>Application Type:</b>	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	17618CON6_Response_Declaration.pdf	3198142 5d2e6d174722da50267f907bd71772487c5c76d1	no	7

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**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.

**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 01/28/2014  
**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)
January 28, 2014	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/961,828	08/07/2013	Andrew Acheampong	17618CON6 (AP)	9904

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	04/28/2014

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 08-0114 (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  
 Applicant asserting small entity status. See 37 CFR 1.27  
 Applicant changing to regular undiscounted fee status.

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.

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.

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 January 28, 2014  
 Typed or printed name Laura L. Wine Registration No. 68681

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	13961828			
<b>Filing Date:</b>	07-Aug-2013			
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS			
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong			
<b>Filer:</b>	Laura Lee Wine/Maria Stein			
<b>Attorney Docket Number:</b>	17618CON6 (AP)			
Filed as Large Entity				
<b>Utility under 35 USC 111(a) Filing Fees</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
Utility Appl Issue Fee	1501	1	960	960
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>960</b>



## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	18049823
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Maria Stein
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	28-JAN-2014
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	16:59:09
<b>Application Type:</b>	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	3514
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 1.20 (Post Issuance fees)

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

<b>File Listing:</b>					
<b>Document Number</b>	<b>Document Description</b>	<b>File Name</b>	<b>File Size(Bytes)/ Message Digest</b>	<b>Multi Part /.zip</b>	<b>Pages (if appl.)</b>
1		17618CON6_Response_and_iss uefees.pdf	250180 <small>dcc429179413e39e8701861024a9423d6af7cf11</small>	yes	5
<b>Multipart Description/PDF files in .zip description</b>					
<b>Document Description</b>			<b>Start</b>	<b>End</b>	
Miscellaneous Incoming Letter			1	4	
Issue Fee Payment (PTO-85B)			5	5	
<b>Warnings:</b>					
<b>Information:</b>					
2	Fee Worksheet (SB06)	fee-info.pdf	32340 <small>ed01c2a69ea7020ded2b90549d853ed3c9e23021</small>	no	2
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>			282520		
<p>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.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  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.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  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.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  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.</p>					

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Serial No.: 13/961,828

Filed: August 7, 2013

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
CYCLOSPORIN COMPONENTS

Examiner: Marcela M Cordero Garcia

Group Art Unit: 1676

Confirmation No. 9904

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 January 28, 2014, Applicant respectfully submits the following comments.

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

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

**SUMMARY OF TELEPHONE INTERVIEW**

Attendees, Date and Type of Interview

A telephone interview conducted on December 20, 2013 and attended by Examiner Marcela M Cordero Garcia and Laura L. Wine.

Identification of Claims Discussed

The Claims were discussed.

Identification of References Discussed

U.S. Patent Application Serial Nos. 13/649,287, 12/035,698, 13/967,168, 13/967,179, 13/967,189, 13/967,163, and 11/897,177 were discussed.

Principal Arguments and Other Matters

U.S. Patent Application Serial Nos. 13/649,287, 12/035,698, 13/967,168, 13/967,179, 13/967,189, 13/967,163, and 11/897,177 were discussed with regards to potential obviousness-type double patenting. While the Applicants do not acquiesce to any potential obviousness-type double patenting rejections over the claims of these references, in order to expedite prosecution, terminal disclaimers were filed over these copending applications and accepted on December 20, 2013.

Results of Interviews

It was agreed that the Applicants would file terminal disclaimers as discussed above. The Examiner also agreed that the Claims were allowable.

**COMMENTS ON STATEMENTS OF REASONS FOR ALLOWANCE**

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

The Applicants acknowledge the Examiner's withdrawal of the Requirement for Election of Species, mailed October 25, 2013.

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.

Docket No. 17618CON6(AP)

Serial No. 13/961,828

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,

January 28, 2014

/Laura L. Wine /

Laura Wine-T2-7H  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612  
Direct: 714-246-6996  
Fax: 714-246-4249

Laura L. Wine  
Reg. No. 68,681

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Acheampong, *et al.*

Serial No.: 13/961,828

Filed: August 7, 2013

For: METHODS OF PROVIDING  
THERAPEUTIC EFFECTS USING  
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Examiner: Marcela M Cordero Garcia

Group Art Unit: 1676

Confirmation No. 9904

Customer No.: 51957

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Respectfully submitted,

January 28, 2014

/Laura L. Wine /

Laura Wine-T2-7H  
Allergan, Inc.  
2525 Dupont Drive  
Irvine, CA 92612  
Direct: 714-246-6996  
Fax: 714-246-4249

Laura L. Wine  
Reg. No. 68,681

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	18131119
<b>Application Number:</b>	13961828
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9904
<b>Title of Invention:</b>	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
<b>First Named Inventor/Applicant Name:</b>	Andrew Acheampong
<b>Customer Number:</b>	51957
<b>Filer:</b>	Laura Lee Wine/Maria Stein
<b>Filer Authorized By:</b>	Laura Lee Wine
<b>Attorney Docket Number:</b>	17618CON6 (AP)
<b>Receipt Date:</b>	06-FEB-2014
<b>Filing Date:</b>	07-AUG-2013
<b>Time Stamp:</b>	12:54:13
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	17618CON6INTERVIEWSUMMARYANDRESPONSETOREASONSFORALLOWANCE.pdf	121698 <small>bda92f3415da0f077b1445610e5d1e9b6af1d2e1</small>	no	4

### Warnings:

### Information:

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.
13/961,828	04/01/2014	8685930	17618CON6 (AP)	9904

51957 7590 03/12/2014  
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, Assignee (with 37 CFR 1.172 Interest);  
Andrew Acheampong, Irvine, CA;  
Diane D. Tang-Liu, Las Vegas, NV;  
James N. Chang, Newport Beach, CA;  
David F. Power, Hubert, NC;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit [SelectUSA.gov](http://SelectUSA.gov).

AO 120 (Rev. 08/10)

TO: <b>Mail Stop 8</b> <b>Director of the U.S. Patent and Trademark Office</b> P.O. Box 1450 Alexandria, VA 22313-1450	<b>REPORT ON THE                  FILING OR DETERMINATION OF AN                  ACTION REGARDING A PATENT OR                  TRADEMARK</b>
---	--

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District of Texas, Marshall Division on the following  
 Trademarks or  Patents. (  the patent action involves 35 U.S.C. § 292.):

DOCKET NO. 2:14-cv-638	DATE FILED 5/22/2014	U.S. DISTRICT COURT Eastern District of Texas, Marshall Division
PLAINTIFF ALLERGAN, INC.		DEFENDANT ACTAVIS PLC, ACTAVIS, INC., WATSON LABORATORIES, INC., and ACTAVIS PHARMA, INC.
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,633,162	1/21/2014	Allergan, Inc.
2 8,642,556	2/4/2014	Allergan, Inc.
3 8,648,048	2/11/2014	Allergan, Inc.
4 8,685,930	4/1/2014	Allergan, Inc.
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY <input type="checkbox"/> Amendment <input type="checkbox"/> Answer <input type="checkbox"/> Cross Bill <input type="checkbox"/> Other Pleading		
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK	
1			
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
--------------------

CLERK	(BY) DEPUTY CLERK	DATE
-------	-------------------	------

Copy 1—Upon initiation of action, mail this copy to Director    Copy 3—Upon termination of action, mail this copy to Director  
 Copy 2—Upon filing document adding patent(s), mail this copy to Director    Copy 4—Case file copy