Cross-Discipline Team Leader Review

Date	September 4, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 22-369
Applicant	Allergan, Inc.
Date of Submission	March 4, 2014
PDUFA Goal Date	September 4, 2014
Type of Application	Supplement 10 incorporating revisions to Supplement 8
Name	Latisse (bimatoprost ophthalmic solution) 0.03%
Dosage forms / Strength	Topical ophthalmic solution
Indication(s)	For the treatment of hypotrichosis of the eyelashes
Recommended:	Recommended for Approval

1. Introduction

Prior Approval Supplement S-010 submitted on 03 March 2014, received 04 March 2014, proposed revisions to the U.S. Package Insert for Latisse (bimatoprost ophthalmic solution) 0.03% to encompass Agency-requested potential labeling for pediatric use. Allergan amended the supplemental application in a submission dated 01 April 2014, explaining that the company believes that the FINAL Clinical Study Report for Study 192024-040 submitted on 27 March 2013, addresses NDA 22-369 Postmarketing Commitment #1 in the context of the Pediatric Research Equity Act (PREA). The labeling submitted, updates the U.S. Package Insert to incorporate pediatric patients. Protocol 192024-040 was originally submitted on 24 November 2009. The trial was conducted in order to fulfill the PREA requirement. The Agency agreed with the protocol.

Bimatoprost is an efficacious ocular hypotensive agent which was first approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in March 2001 (NDA 21-275, Lumigan (bimatoprost ophthalmic solution), 0.03%). The mechanisms of action by which bimatoprost reduces intraocular pressure are believed to be by increasing aqueous humor outflow through the trabecular meshwork and by enhancing uveoscleral outflow.

In the initial NDA 21-275 submission, increased eyelash growth was observed as an adverse event in the clinical trials of bimatoprost 0.03% ophthalmic solution used once daily. In two active-controlled Phase 3 studies, eyelash growth was reported as an adverse event after 3 months of treatment in 17.9% and 25.6% of patients receiving bimatoprost 0.03% ophthalmic solution once daily, applied to the conjunctival sac. The proportion of subjects reporting eyelash growth increased after 6 and 12 months of treatment.

In a proof-of-concept study evaluating the effect of bimatoprost 0.03% on eyelash growth, color, and thickness, after being applied to the upper eyelid, bimatoprost was shown to be effective as measured by subjects' assessment of change from baseline. At the end of the 3-month treatment period, 81% (13/16) of subjects who completed the study reported their overall eyelash appearance to be "much improved," and 19% of subjects reported their overall eyelash appearance to be "improved."

The original NDA 22-369 application was approved December 24, 2008. The indication of hypotrichosis of the eyelid had been studied under IND 48,929 with endpoints including eyelash length, progressive eyelash thickness/fullness, and eyelash darkness/intensity. The efficacy is summarized in the tables below. The safety was supported by both data in NDA 22369 and NDA 21275. The application was the subject of an Advisory Committee in which the application was recommended to be approved.

GEA Score Description of Eyelash Prominence
1 Minimal (includes everything up to minimal)
Corresponding to photoguide grade 1 frontal and superior views
2 Moderate
Corresponding to photoguide grade 2 frontal and superior views
3 Marked
Corresponding to photoguide grade 3 frontal and superior views
4 Very Marked (includes very marked and above [includes best possible])
Corresponding to photoguide grade 4 frontal and superior views

Analysis of Primary Endpoint

Number (%) of Subjects with At Least a 1-Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

Visit [a]	Bimatoprost 0.03% (N=137)	Vehicle (N=141)	p-value [b]
Week 1	7/137 (5)	3/141 (2)	0.2124 [c]
Week 4	20/137 (15)	11/141 (8)	0.0719
Week 8	69/137 (50)	21/141 (15)	<0.0001
Week 12	95/137 (70)	28/141 (20)	<0.0001
Week 16 (Primary Endpoint)	**107/137 (78)**	**26/141 (18)**	**<0.0001**
Week 20	103/131 (79)	27/126 (21)	<0.0001

a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
b P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of <5.
c Fisher's exact test was performed.

Number (%) of Subjects with At Least a 2-Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

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a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
b P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of <5.
c Fisher's exact test was performed.

The approval letter included a requirement for a pediatric study under PREA in pediatric patients 0 to 17 years of age. Allergan committed to conduct "A controlled trial of at least 4 months duration with Latisse (bimatoprost ophthalmic solution) 0.03% in at least 30 pediatric subjects less than 18 years of age with hypotrichosis due to a medical condition with the primary endpoint of a 1-grade increase in GEA from baseline." The dates for these were:

Protocol Submission: November 30, 2009
Study Start: June 30, 2010
Final Report Submission: December 31, 2012.

Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03% studied in this supplemental NDA are the same drug product.

2. Background

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March 7, 2013, NDA 22-369, S-008 was received which provided for revisions to the 5.8 Use with Contact Lenses, 6.1 Clinical Studies Experience, 6.2 Postmarketing Experience, 16 How Supplied/ Storage and Handling and 17.8 /Patient Counseling /Use with Contact Lenses sections of the Package insert.

March 27, 2013 – NDA 22-369 Submission of Final Study Report, 192024-040 in order to fulfill Postmarketing Requirement under PREA.

January 28, 2014 – Preliminary Comments for IND 109,930 Pre-NDA Meeting. (b) (4) he Agency commented, *"In light of the data collected in Study 192024-040, proposed labeling may need to encompass children 5 years of age and older.* (b) (4) ."

January 29, 2014 – IND 109,930 Pre-NDA Meeting. The Agency confirmed that pursuant to recommendations from the Pediatric Review Committee (PeRC), the data from Study 192024-040 is likely to be included in the Latisse Rx label. (b) (4)

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February 3, 2014 – Email Communication. The Agency again confirmed that Allergan should submit an NDA supplement proposing revised pediatric labeling which should either resubmit the study report or reference the earlier submission.

February 11, 2014- Complete Response letter for Supplement 8. The Agency suggested revised labeling incorporating some of the changes proposed by Allergan.

Reviewer's Comment:
Pediatric study reports in response to PREA post-marketing requirements are required to be submitted and the findings of the studies included in the product labeling.

3. CMC

This supplemental application proposes no revisions to the Chemistry Manufacturing information for the Latisse new drug application.

4. Nonclinical Pharmacology/Toxicology

From the 6/25/14 Nonclinical Pharmacology/Toxicology review:

No new nonclinical studies were submitted with this efficacy supplement. As such, there are no new concerns from the nonclinical perspective. However, we have the following recommendation for the package insert. Section 13.1 of the Latisse package insert should include the exposure margin based on blood levels (AUC), as appears in the approved Lumigan label *(added text shown in italics):*

> *"Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels)."*

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics studies were submitted with this supplemental application.

6. Sterility Assurance

This supplemental application proposes no revisions to the Chemistry Manufacturing information for the Latisse new drug application.

7. Clinical/Statistical - Efficacy

From the Medical Officer Review finalized 6/24/14:

This supplemental NDA contains the clinical study report of 192024-040: A Multicenter, Double-Masked, Randomized, Parallel-Group Study Assessing the Safety and Efficacy of Once Daily Application of Bimatoprost Solution 0.03% Compared to Vehicle When Applied to the Eyelid Margins of Pediatric Subjects.

Study No.	Study Design	Main Entry Criteria	Study Objectives	# Pts Treated, Treatment	Duration of Treatment	Key Results
192024-040	Phase 4 multicenter, double-masked, randomized, vehicle-controlled parallel-group study	Pediatric subjects 5 to 17 years of age who were post chemotherapy or had alopecia areata; or Healthy adolescent subjects, 15 to 17 years of age with baseline overall eyelash prominence of minimal , moderate or marked based on the 4-point Global Eyelash Assessment Scale	To evaluate the safety and efficacy of bimatoprost solution 0.03% once daily compared with vehicle in increasing overall eyelash prominence following topical administration to the upper eyelid margins in the pediatric population	71 randomized 48 bimatoprost 23 vehicle Bimatoprost or vehicle applied once daily to the upper eyelid margins using a single-use-per-eye applicator	16 weeks (treatment period) followed by a 4-week posttreatment follow-up period	(b) (4) Bimatoprost solution 0.03% was well-tolerated.

Study 192024-040

This was a multicenter, double-masked, randomized, vehicle-controlled, parallel-group study consisting of approximately 6 or 7 scheduled visits and 1 telephone visit (screening, baseline [or a single screening/baseline combined visit], telephone visit [week 1], and months 1, 2, 3, 4 [or early exit], and 5 [post treatment follow-up]). A subject was considered to have entered the study at the time of randomization on day 1. Qualified subjects were randomly assigned to daily bilateral application to the upper eyelid margins with either bimatoprost solution 0.03% or vehicle in a 2:1 ratio.

Approximately 70 subjects (approximately 30 medical-need post chemotherapy or alopecia areata pediatric subjects and approximately 40 nonmedical-need[1] adolescents) were planned to be enrolled at approximately 15 investigational sites. At the time of randomization, eligible subjects were stratified by age group (5 to 11 versus 12 to 17 years). Seventy-one subjects were randomized and enrolled in the study.

There were 40 nonmedical-need adolescent subjects, 16 post chemotherapy subjects, and 15 subjects with alopecia areata. The mean age overall was 14.5 years (range 5 to 17 years).

Table 6.1.2 -1 Demographics and Baseline Characteristics

Characteristic	Bimatoprost 0.03% (N=48)	Vehicle (N=23)
Age		
5 – 11 years	6 (12.5%)	3 (13.0%)
12 – 17 years	42 (87.5%)	20 (87.0%)
Sex		
Male	11 (22.9%)	7 (30.4%)
Female	37 (77.1%)	16 (69.6%)
Iris Color		
Dark [a]	34 (70.8%)	11 (47.8%)
Light [b]	14 (29.2%)	12 (52.2%)
GEA Score		
Minimal (1)	10 (20.8%)	9 (39.1%)
Moderate (2)	11 (22.9%)	1 (4.3%)
Marked (3)	27 (56.3%)	13 (56.5%)
Very Marked (4)	0	0
Etiology		
Post chemotherapy	13 (27.1%)	3 (13.0%)
Alopecia areata	9 (18.8%)	6 (26.1%)
Healthy adolescent	26 (54.2%)	14 (60.9%)

a brown and dark brown

b blue, blue-gray, blue/gray-brown,gray, green, green-brown, hazel, and other.

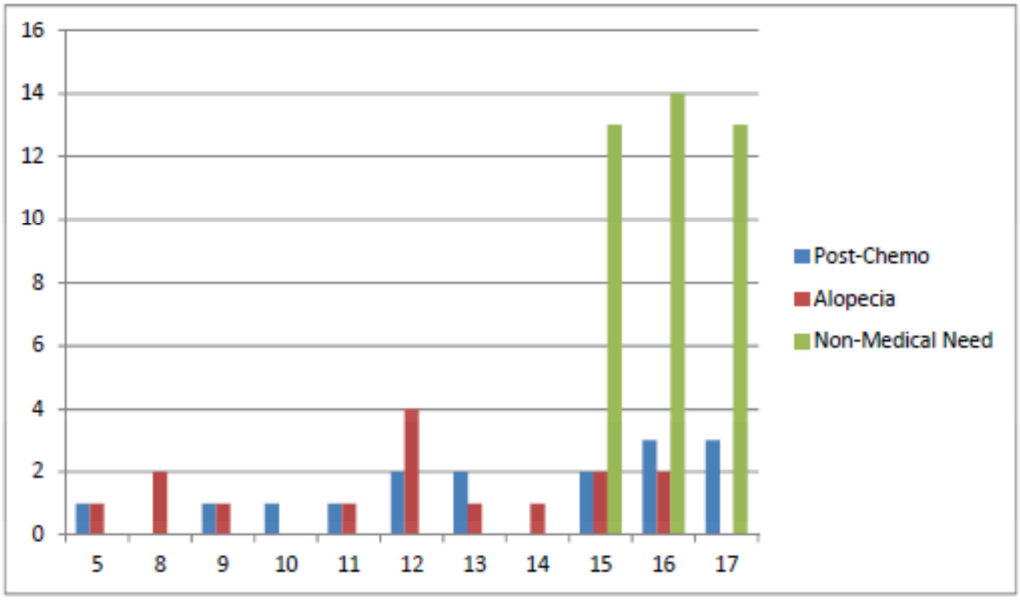
1 Nonmedical need is defined as hypotrichosis with no identifiable causal related medical condition

Table 6.1.2-2 Sample Size of Each Etiology by Age Group (ITT Population)

Age Group	Postchemotherapy (N=16)		Alopecia Areata (N=15)		Non-medical Need (N=40)		Overall Population (N=71)	
	Bim	Veh	Bim	Veh	Bim	Veh	Bim	Veh
5 to 11	3	1	3	2	0	0	6	3
12 to 14	3	1	3	3	0	0	6	4
15 to 17	7	1	3	1	26	14	36	16

Bim= bimatoprost 0.03% treatment; Veh= vehicle treatment

Figure 6.1.2-1 Frequency Distribution of Study Population by Age



There were imbalances in the patient population by age group and by etiology which were caused by difficulty enrolling postchemotherapy and alopecia areata patients.

In order to increase enrollment, non-medical need adolescent subjects were enrolled. Thus, the majority of the resulting study population was age 15 to 17 (n=52, 73.2%).

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	Age Range (years)	LATISSE®	Vehicle	Difference (95% CI)
Adolescents with hypotrichosis (N=40)	15 – 17	19/26 (73%)	1/14 (7%)	66% (44%, 88%)
Post Chemotherapy Pediatric Patients (N=16)	5 – 17	11/13 (85%)	3/3 (100%)	-15% (-35%, 4%)
Alopecia Areata Pediatric Patients (N=15)	5 – 17	4/9 (44%)	2/6 (33%)	11% (-39%, 61%)

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8. Safety

From the Medical Officer Review finalized 6/24/14:

Study 192024-040 is the only study of pediatric subjects with bimatoprost ophthalmic solution 0.03%. Bimatoprost ophthalmic solution has been studied extensively during its clinical development program for the reduction of intraocular pressure and for the treatment of hypotrichosis in adults.

	Postchemotherapy Pediatric Subjects		Alopecia Areata		Non-medical Need	
	Bim 0.03% N=13	Veh N=3	Bim 0.03% N=9	Veh N=6	Bim 0.03% N=26	Veh N=14
Median study duration (days)[a]	149.0	148.0	151.0	154.5	149.5	151.0
Mean duration of treatment exposure (days)	121.2	117.0	118.1	120.2	117.3	119.8

a Duration was calculated from date of month 5 or early termination minus date of day 1 (baseline) plus 1.
b Treatment exposure was calculated from date of last dose minus date of day 1 (baseline) plus 1. If date of last dose was missing, last visit recorded for GEA was used.
Source: CSR Tables 14.6-4.1 to 14.6-5.3

Deaths
None.

Nonfatal Serious Adverse Events
None.

Ocular and Non-ocular Serious Adverse Events
None.

Dropouts and/or Discontinuations
One nonmedical need adolescent in the bimatoprost treatment group discontinued treatment due to an adverse event – exacerbation of eczema on face.

Common Adverse Events

Table 7.4.1-1 All Adverse Events with Incidence > 1 Subject in Either Treatment Group Treatment and Posttreatment Periods Combined (Safety Population)

Adverse Event (Preferred Term[a])	System Organ Class	Bimatoprost 0.03% (N=48)	Vehicle (N=23)
Conjunctival hyperemia	Eye Disorders	2 (4.2%)	0 (0.0)
Conjunctivitis	Eye Disorders	2 (4.2%)	0 (0.0)
Eczema	Skin and subcutaneous tissue disorders	2 (4.2%)	0 (0.0)
Erythema of eyelid	Eye Disorders	2 (4.2%)	0 (0.0)
Nasopharyngitis	Infections and Infestations	2 (4.2%)	0 (0.0)
Sinusitis	Infections and Infestations	2 (4.2%)	0 (0.0)

Note: All adverse events, regardless of relationship to treatment , with incidence >1 subject in either treatment group, are presented. Preferred terms are sorted by descending frequency in treatment groups from left to right. Within each preferred term, a subject is counted at most once.
a MedDRA Version 15.1
Source: Table 14.3-5.1

Safety Summary Statement

The adverse event profile is consistent with those reported in previous studies of bimatoprost ophthalmic solution. There were no reports of iris hyperpigmentation or skin hyperpigmentation.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The applicant received a Fulfillment of Postmarketing Requirement letter dated 4/21/14 which stated that postmarketing requirement 501-1 (Deferred pediatric study under PREA for the treatment of hypotrichosis in pediatric patients ages 0 to 17 years) had been fulfilled. Based on the low enrollment in the lower age groups, studies in pediatric patients between ages 0 to less than 5 years would be impossible or highly impractical.

As noted in sections of this review (e.g., Clinical, Statistical), among different individuals within the Agency (b) (4) There were also opinions in between and differences of opinion with respect to the wording to be included in the labeling.

This supplemental application was discussed at the Pediatric Regulatory Committee (PeRC) on Wednesday, August 20, 2014. It was the opinion of the members present that the Section 8.4 of the Latisse package insert be revised to include a description of the efficacy findings for the different populations based on their underlying medical condition from Study 192024-040 without providing interpretations or definitive conclusions. There was a consensus agreement among PeRC members and the Review team to accept this approach. The package insert has been revised based on this recommendation.

CDTL Reviewer Comments:
The revised package insert language for Section 8.4 found in the Appendix of this review represents the recommended pediatric language from PeRC. These edits describe the results from Study 192024-040 in children down to age 5 years. This language is acceptable, although in this reviewer's opinion, the edits to the Latisse Section 8.4 found in the Medical Officer's review dated 6/24/14 would have better represented the summary pediatric information provided by the applicant in S-010 for use by the prescribing physician.

11. Other Relevant Regulatory Issues

OSI
An Office of Scientific Investigations (OSI) audit was requested.

The clinical site of Dr. Baumann was selected for inspection because it was among the highest enrolling sites.

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Leslie S. Baumann, M.D. Baumann Cosmetic and Research Inst. 4500 Biscayne Boulevard Suites 100 and 105 Miami Beach, FL 33137	192024-040/ 10004/ 11	July 2014	NAI. Pending final classification.

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of a regulatory action.

FINANCIAL DISCLOSURE
The applicant has adequately disclosed the financial interests/arrangements with clinical investigators. None of those with significant financial interests are sponsor employees.

Allergan took the following steps to minimize potential bias of clinical study results by any of the investigators:

- The study was randomized and double-masked.
- Efficacy measures included variables derived from information recorded by the patients during the study and also variables which are objectively measured via digital image analysis.
- Investigators were not aware of the randomization block size.
- Study payments were not made contingent upon study results.

There is no evidence suggesting problems with the integrity of the submitted data.

BIOSTATISTICS
Per the Biostatistics review dated 8/5/14:

Study 192024-040 was a multi-center, randomized, vehicle-controlled, double-masked clinical study to investigate the safety and efficacy of bimatoprost solution 0.03% compared with vehicle in pediatric subjects, when applied once-daily bilaterally for four months to the upper eyelid margins. By etiology, there were three different subgroups of pediatric subjects enrolled in this study:

1) Five to 17 years old pediatric subjects who had post chemotherapy eyelash hypotrichosis;
2) Five to 17 years old pediatric subjects with alopecia areata;

3) Fifteen to 17 years old non-medical need adolescent subjects.

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12. Labeling

NDA 22-369/S-008 and S-010 are recommended for approval with the labeling found in the Appendix of this review.

Previous recommendations from the review of NDA 22-369/S-008 have been incorporated in the labeling for supplement NDA 22-369/S-010.

Specifically, supplement S-008, dated and received March 7, 2013, provides for revisions to Section 5.8 Use with Contact Lenses, Sections 6.1 Clinical Studies Experience, 6.2 Postmarketing Experience and Section, , 16 How Supplied/ Storage and Handling, 17.8 /Patient Counseling /Use with Contac Lenses sections of the Package insert. Supplement S-008 was reviewed and issued a complete response letter on February 11, 2014. The labeling for S-010 has been updated to incorporate the following revisions requested in S-008 (deletions are in ~~strikethrough~~ and additions are underlined):

The first sentence of the 5.8 Use with Contact Lenses section is revised as follows:

> **LATISSE®** contains benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses.

The second paragraph in the 6.1 Clinical Studies Experience section is revised as follows:

> The most frequently reported adverse ~~events~~ reactions were eye pruritus, conjunctival hyperemia, skin hyperpigmentation, ocular irritation, dry eye symptoms, and periorbital erythema ~~of the eyelid~~. These ~~events~~ reactions occurred in less than 4% of patients.

The second sentence in the 6.2 Postmarketing Experience section, is revised as follows:

> The following reactions have been identified during postmarketing use of **LATISSE®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting possible causal connection to **LATISSE®**, or a combination of these factors, include: eye swelling,

eyelid edema, hypersensitivity (local allergic reactions), lacrimation increased, madarosis and trichorrhexis (temporary loss of a few lashes to loss of sections of eyelashes, and temporary eyelash breakage, respectively), periorbital and lid changes associated with a deepening of the eyelid sulcus, rash (including macular, erythematous), skin discoloration (periorbital), and vision blurred.

The statement in 16 How Supplied / Storage and Handling is revised as follows: Storage: ~~LATISSE® should be stored~~ Store at 2-25 ºC (36-77 ºF).

The 17.8 Use with Contact Lenses section of the Patient Counseling Information is revised as follows:

Patients should be advised that **LATISSE®** solution contains benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses. Contact lenses should be removed prior to application of **LATISSE®** and may be reinserted 15 minutes following its administration.

The labeling received by the FDA Gateway as dated September 4, 2014, includes the revisions to Section 8.4 for supplement S-010 and revisions to Sections 5.8, 6.1, 6.2, 16 and 17.8 requested for supplement S-008.

Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-369/S-008 and S-010 are recommended for approval with the draft labeling found in the Appendix of this review.

It is recommended that the Agency waive the requirement for studies in pediatric patients between ages 0 to <5 years because such studies would be impossible or highly impractical. Studies in children 5 years or greater have been completed.

Appendix 1

NDA 22-369/S-010 is recommended for approval with the draft labeling found in the Appendix of this review.

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/s/

WILEY A CHAMBERS
09/04/2014
For William Boyd, MD