CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209569Orig1s000

SUMMARY REVIEW

Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review of NDA 209569

Date	December 16, 2019
From	Peter Stein, M.D., Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review
NDA #	NDA 209569
Applicant	Dutch Ophthalmic, USA (DORC)
Date of Submission	April 29, 2019
PDUFA Goal Date	December 29, 2019
Proprietary Name	TissueBlue 0.025%
Established or Proper Name	Brilliant Blue G Ophthalmic Solution
Dosage Form(s)	Intraocular solution
Proposed Dosing Regimen(s)	TissueBlue 0.025% is carefully injected into the Balanced Salt Solution (BSS)-filled vitreous cavity using a blunt cannula attached to the pre-filled syringe, without allowing the cannula to contact the retina or allowing TissueBlue to get under the retina. Sufficient staining is expected within a few seconds. Following staining, all excess dye should be removed from the vitreous cavity.
Regulatory Action	Approval
Proposed Indication(s)/Population(s)	For use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Wiley Chambers
Statistical Review	N/A
Pharmacology Toxicology Review	Maria Rivera
OPQ Review Drug Substance	Sharon Kelly
OPQ Review Drug Product	Milton Sloan
OPQ Microbiology Review	Jainli Xue
Clinical Pharmacology Review	N/A
OPDP	Carrie Newcomer
OSI	N/A
CDTL Review	William M. Boyd
OSE/DEPI	N/A
OSE/DMEPA	Maximilian Straka
OSE/DRISK	Carlisha Gentles

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Summary

Surgical treatment of certain macular conditions, such as surgery for macular holes can be aided by peeling/removing of the internal limiting membrane. The internal limiting membrane is naturally transparent. Staining of the internal limiting membrane provides a means of visualizing the membrane and facilitating its removal.

Brilliant Blue G is a common laboratory reagent used for protein visualization during gel electrophoresis or quantitation (Bradford assay). (b) (4) marketed in the European Union as a device since 2007 for visualizing the internal limiting membrane. The dye forms a stable negatively charged complex with basic amino acid residues of proteins, mainly arginine and aromatic amino acids. The stained membrane is easier to visualize for removal.

The Food Drug and Cosmetic Act classifies the product as a drug product because there is selective staining of tissues (chemical action within the body). This is a 505(b)(2) application relying on published literature. The applicant has not conducted or sponsored any clinical studies of this product; however, clinical studies using this particular product have been conducted by individual clinicians and published. Additional clinical trials using the same molecular entity but manufactured by different companies have also been published. Since the published clinical trials were not conducted or sponsored by any company, none of the companies who market Brilliant Blue have a right to reference the studies.

2. Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
Surgical procedures of the macular, particularly macular holes often include removal of the internal limiting membrane. The internal limiting membrane is transparent and difficult to remove unless it can be visualized. Brilliant Blue G stains the internal limiting membrane allowing the membrane to be visualized and removed. The benefit-risk ratio of removing the internal limiting membrane is enhanced through the use of Brilliant Blue G staining.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Surgical procedures of the macular including macular holes may include removal of the internal limiting membrane. • The internal limiting membrane is transparent and difficult to remove unless it can be visualized. Removal of the internal limiting membrane can be beneficial in performing macular surgery.	Visualization of the internal limiting membrane is necessary in the removal of the internal limiting membrane. Brilliant blue G staining of the internal limiting membrane is one method of visualizing the internal limiting membrane.
Current Treatment Options	• Trypan blue and indocyanine green are used off-label to stain the internal limiting membrane. Pharmacy compounded Brilliant Blue G is currently used to stain the internal limiting membrane.	There are no dyes currently approved to stain the internal limiting membrane. Quality control benefits may be improved with a marketed approved product compared to a compounded product.
Benefit	• Brilliant Blue G stains the internal limiting membrane. Removal of the internal limiting membrane can be accomplished when the membrane can be visualized.	The internal limiting membrane can be visualized with Brilliant blue G. Improved visualization can be expected to improve the safety of the surgical procedure.
Risk and Risk Management	• Adverse events in the clinical trials reported in the literature were minimal.	Brilliant Blue G has a relatively safe profile.

3. Background

There are no products approved for this indication. Trypan blue and indocyanine green are used off-label to stain the internal limiting membrane. Compounded BBG is used to stain the internal limiting membrane. Removal of the internal limiting membrane is recommended in some surgical situations to improve visual function.

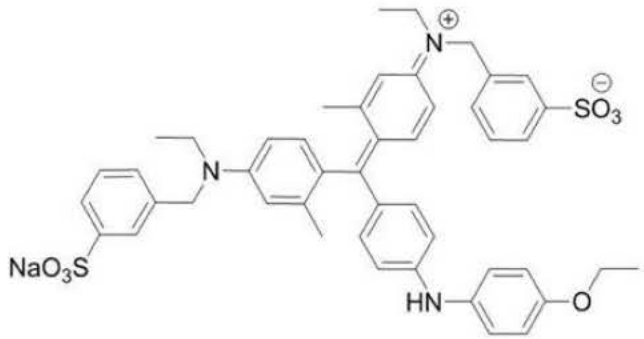
On May 15, 2015, Brilliant Blue G (BBG) was nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Brilliant Blue G was identified in the nominations as a dye to be used in staining for visualization during ophthalmic procedures. Effective March 21, 2019, Brilliant Blue G was added to the list of bulk drug substances that can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

In 2012, the FDA's Office of Orphan Products Development (OOPD) granted an orphan designation for Brilliant Blue G 0.025% Solution "to selectively stain the [redacted (b) (4)] internal limiting membrane (ILM) [redacted (b) (4)] to DORC. In a subsequent correspondence to the applicant dated June 26, 2019, the designation of brilliant blue G was modified by OOPD to "for use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane."

4. Product Quality

IUPAC: Sodium;3-[[4-[(Z)-[4-(4-ethoxyanilino)phenyl]-[4-[ethyl-[(3 sulfonatophenyl)methyl]azaniumylidene]-2-methylcyclohexa-2,5-dien-1-ylidene]methyl]-N-ethyl-3-methylanilino]methyl]benzenesulfonate

Laboratory Code: BBG, Brilliant Blue G



Molecular Formula: $C_{47}H_{48}N_3NaO_7S_2$ Relative Molecular Mass: 854.02 g/mol

DRUG SUBSTANCE

The synthesis of the drug substance consists of [redacted] The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control.

Specifications for Brilliant Blue G Drug Substance

Tests	Specification		
Appearance	Dark blue to copper brown powder		
Identification (FT-IR)	Conforms to reference spectrum		
Identification (HPLC)	Retention time of the sample corresponds to that of the standard		
Assay (HPLC)	[redacted]		
Purity (HPLC)			
Impurities (HPLC)	**Impurity**	**RRT**	**Specification**
	Impurity [redacted]		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Impurity		NMT [redacted]%
	Unspecified, Unidentified Impurities		NMT [redacted]%
	Total Impurities		NMT [redacted]%
Water Content (KF)	NMT [redacted]%		
Residual Solvents (GC)	[redacted]		
[redacted]			
Elemental Impurities (ICP-MS)			
Microbial Limits	Total aerobic microbial count: NMT [redacted] CFU/g Total yeast and mold count: NMT [redacted] CFU/g		
Endotoxin	NMT [redacted] EU/mg		

Source: Module 3.2.S.4.1

DRUG PRODUCT

Brilliant Blue G 0.025% Solution, with a proposed proprietary name of TissueBlue, is a sterile, stable, single-dose ophthalmic solution formulation containing 0.025% Brilliant Blue G.

Composition of Brilliant Blue G 0.025% Solution

Component	% w/w	Function	Compendial
Brilliant Blue G (BBG)	0.025	Active Ingredient	Noncompendial
Polyethylene Glycol (PEG) 3350	(b) (4)		USP/NF
Buffered Sodium Chloride solution*			Noncompendial

Source: Module 3.2.P.1

Brilliant Blue G 0.025% Solution will be (b) (4) and supplied sterile in a single-use Luer Lok, 2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod packed in a preformed polypropylene blister sealed with a Tyvek® (b) (4)

BBG compounded with (b) (4), polyethylene glycol (PEG), (b) (4) will sink to the back of the eye where the staining is needed. (b) (4)

(b) (4)

marketed by DORC outside the United States and was used in some of the clinical trials described in this review.

***Buffered NaCl Solution is composed of the following:**

(b) (4) mg Sodium Chloride, CAS 001310732
mg Sodium Phosphate Dibasic (b) (4) CAS 010028247
mg Sodium Phosphate Monobasic Dihydrate, CAS 013472350
Water for Injection

Drug Product Specifications

Test	Specification
Appearance	Transparent, Bright Blue
Identity (HPLC - UV/VIS)	Complies to Reference Spectrum
BBG Assay (HPLC)	(b) (4) % of the declared content
Impurities (HPLC)[1]	(b) (4)
Impurity (b) (4)	≤ (b) (4) %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurity	≤ %
Impurit	≤ %
Impurity	≤ %
Any Unknown Impurity	≤ %
Total Impurities	≤ (b) (4) %
Ratio of (b) (4)	(b) (4)
Fill Volume	
Product Sterility	Sterile
Exterior Sterility	Sterile
Endotoxins	(b) (4)
Particulate Matter	
Osmolality	
PEG Content	
Final packaging control	According to (b) (4)

[1] Impurities (b) (4) are known from the drug product; Impurities (b) (4) are known from BBG drug substance.

[2] RRT = Relative retention time

Source: Module 3.2.S.5.1

Drug Product Container Closure

The drug product will be (b) (4) supplied sterile in a single-use Luer Lok, 2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod packed in a pre-formed polypropylene blister sealed with a Tyvek® lid (Figure 1).

Figure 1
Packaging System for TissueBlue (without Tyvek Lid)

Source: Module 3.2.P.7

Five sealed blisters will be packed into a carton which will contain:

- sealed blisters
- copy of the Prescribing Information
- Patient Record Labels
- Secondary Label (applied over the edge of the box (b) (4)).

INSPECTIONAL ACTIVITIES

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 9/9/2019.

Facility Status	Completion Date	Facility ID	Facility Name
Approve Facility			(b) (4)
Approve Facility			
Approve Facility			
No Evaluation Necessary			
Approve Facility			
Approve Facility			
Approve Facility			
Approve Facility			

CMC POST-MARKETING COMMITMENTS
From the original Office of Product Quality Review dated 10/7/2019:

The following PMCs recieved concurrence from the applicant on Oct 3, 2019. An expiration date of 12 months is granted when stored at 15 °C- 25 °C. Both the PMCs and the expiration date should be included in the Action Letter:

1. Post Marketing Commitment # 3724-1: Provide 12-month stability update for Batch 14218 and 6-month stability data for Batch 21618. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

2. Post Marketing Commitment # 3724-2: Any further extension of the expiration date post-approval will need to be submitted for review as a PAS supplement. Final protocol submission date: May 15, 2020; study completion: April 15, 2021; and final report submission: May 15, 2021.

3. Post Marketing Commitment # 3724-3: A leachable study on at least one stability Batch 14618 should be conducted through its expiration date. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

> **Note:** PMC #4 below was requested by Clinical and is not cited in the Product Quality Review dated 10/7/2019. In an email dated December 03, 2019, the applicant and manufacturer, (b) (4) noted a problem in attemptiong to address the Agency's request for a linear barcode on the Tyvek blister. After printing samples, it became clear that the material of the Tyvek lid did not support a consistently readable barcode. The applicant and manufacturer committed to continue to evaluate methods for addressing this in the future but at this time requested an exemption per 21 CFR 201.25 (d). This plan is acceptable.

4. Post Marketing Commitment # 3724-4: Develop a consistently readable barcode on the Tyvek blister for the TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% product. Final report submission: December 31, 2020.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 10/9/2019:
The nonclinical support comes from applicant-owned studies and scientific publications evaluating the toxicity of BBG in various cell and animal models. There is no listed drug for this application.

The ocular toxicity was evaluated after a single intravitreal (IVT) or subretinal injection in rabbits of a BBG formulation (not the clinical formulation) with an observation period of 14 days. Key findings included:

- In eyes treated by subretinal administration, anterior segment inflammation, vitreous opacity and/or presence of vitreal hemorrhage was reported in saline control and BBG-treated groups. However, the increased incidence and/or severity in BBG-treated groups suggests a contribution by the test article.

- Reductions in scotopic a-wave and/or b-wave amplitude at both test-article routes of administration and at both dose levels. The reduction of the ERG amplitudes could be in part related to absorption of the applied light by the dye before the dye reaches the retina. Similar findings were observed in in vitro studies from the published literature and found to be reversible after a washout period.

- In eyes treated by subretinal administration, minimal to marked microscopic retinal changes (detachment and degeneration) were observed. These changes were present in both control and treated groups, but with increased severity in test article-treated groups. Therefore, a contribution by the test article cannot be ruled out.

- Plasma concentrations of BBG from 24 hours postdose through Day 14 were below the limit of quantitation (< 10 ng/mL) for both intravitreal and subretinal route of administration. At the same timepoint, high levels of BBG were still measured in the eye, particularly in the retina and choroid.

At the intended clinical dose regimen, the total dose to be administered to the human eye is 0.125 mg. Therefore, there is no exposure margin at any of the doses used in the animal ocular toxicity study (≤50 µg/eye). Based on the fact that most of the dye is removed from the eye during the ILM peeling procedure, the design of the ocular toxicity study maximizes exposure to the dye and is considered adequate for risk assessment.

A limitation of the ocular toxicity study is that it was conducted with a purified BBG preparation (DYME) (b) (4). The composition of the DYME preparation is different than that of the intended clinical product. However, there is marketing experience with the proposed formulation to support its safe use in humans.

The applicant provided a review of scientific publications of in vitro as well as in vivo studies with BBG. Overall, these studies support the safety of the intended clinical concentration (0.025% or 0.25 mg/mL) and short-term ocular exposure.

The pharmacology/toxicology reviewer believes that the nonclinical study reports provided, the nonclinical literature cited, together with the existent marketing experience for Brilliant Blue G 0.025% Solution (over (b) (4) units distributed in Europe; marketed as ILM-Blue® outside of the United States), provide adequate safety support for the approval of Brilliant Blue G 0.025% Solution for the intended indication. Approval is recommended.

6. Clinical Pharmacology

The drug product is administered locally on the internal limiting membrane. Excess dye is removed by the irrigation/aspiration surgical equipment and/or with the internal limiting membrane when the limiting membrane is removed. There is no additional action on any other structures.

7. Clinical Microbiology

Not applicable. This product is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 10/3/2019:

Clinical Studies

Published clinical trials demonstrate the effectiveness of Brilliant Blue G when used for visualization during ophthalmic procedures. A Medline Search of the medical literature was conducted in March 2015 and September 2019 using the terms: *brilliant blue* and *eye*. There were numerous articles supporting the efficacy of Brilliant Blue G for use in staining for visualization during ophthalmic procedures. There were no articles suggesting that it was not effective. The published reports range from a Meta-analysis of prior literature studies, individual studies and a clinical example demonstrating the visualization of the internal limiting membrane. This list is a representative sample of the 18 clinical trials (12 were controlled clinical trials).

The safety and efficacy of Brilliant Blue G dye is supported by clinical trials conducted with the applicant's product and trials utilizing the same drug substance, (b) (4) The trials conducted with the applicant's Brilliant Blue G can be considered sufficient on their own to support this new drug application. The trials (b) (4) are supportive of the safety and efficacy of the drug product. The trials conducted with drug product in which the source cannot be identified can be considered supportive of the safety and efficacy of the new drug application.

Study #1: Brilliant Blue G-Assissted Internal Limiting Membrane Peeling for Macular Hole: A Systematic Review of the Literature and Meta-Analysis[1]

MEDLINE, EMBASE and Conchrane Central Register of Controlled Trials were systematically reviewed. Outcome measures were the primary closure rate and postoperative best-corrected visual acuity. All studies were of a retrospective design except Fu [randomized] and Machida [randomized]. The source of the BBG is listed in the table.

Author	Dye	N	Age (mean)	Surgical Procedure	Follow-up
Fukuda et al	BBG, 0.25 mg/mL (Sigma-Aldrich) ICG, 1.25 mg/mL	31 22	67 68	25 G PPV+ PEA+IOL	6
Kumar et al	BBG, 0.5 mg/mL (Aurolab) TA	47 47	61 60	23 G PPV, 25% SF6	12
Shukla et al	BBG, 0.5 mg/mL (Aurolab) TB, 0.15% ICG, 5 mg/mL	15 20 15	60 59 59	20/23 G PPV+PEA+IOL, 16% C3F8/20% SF6	6
Baba et al	BBG, 0.25 mg/mL (DORC) ICG, 1.25 mg/mL	35 28	67 66	23 G PPV+PEA+IOL, air	6
Selton et al	BBG (Full article not available) No dye	20 20	NR	NR	6
Williamson & Lee	BBG (Source not identified) ICG, 0.5 mg/mL	109 209	69	20/23 G PPV, PEA+IOL (70%)	6
Fu*	BBG, 0.25 mg/mL (Article not available) No dye	42 41	57	PPV, C3F8	6
Mochizuki et al	BBG, 0.25 mg/mL (Source not identified) ICG, 2.5 mg/mL TA	15 61 21	69 66 63	25G PPV, 20% SF6/12% C3F8/air	12
Machida et al	BBG, 0.25 mg/mL (Sigma-Aldrich) ICG, 2.5 mg/mL TA	16 16 16	64	PPV+PEA+IOL, 20% SF6	12

IOL=intraocular lens implantation, NR=not reported, PEA=phacoemulsification, PPV=pars plana vitrectomy, TA=triamcinolone, TB=trypan blue, BBG=Brilliant Blue G.

*Article not found on internet search.

Brilliant Blue G was source from a variety of suppliers in these clinical trials including the applicant (b) (4)

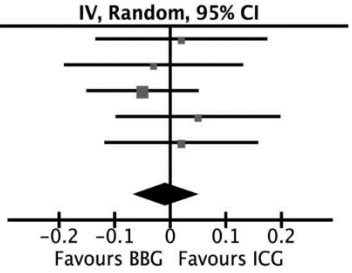
[1] **RETINA** 36:851-858, 2016

Primary Closure Rate

BBG vs ICG

	BBG			ICG				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fukuda, 2011[18]	0.61	0.29	31	0.59	0.27	22	15.0%	0.02 [-0.13, 0.17]	
Baba, 2012[21]	0.79	0.33	35	0.82	0.31	28	13.8%	-0.03 [-0.19, 0.13]	
Williamson, 2013[23]	0.93	0.4	109	0.98	0.47	209	35.9%	-0.05 [-0.15, 0.05]	
Machida, 2014[26]	0.63	0.22	16	0.58	0.2	16	16.4%	0.05 [-0.10, 0.20]	
Mochizuki, 2014[25]	0.86	0.22	15	0.84	0.31	61	18.9%	0.02 [-0.12, 0.16]	
Total (95% CI)			**206**			**336**	**100.0%**	**-0.01 [-0.07, 0.05]**	

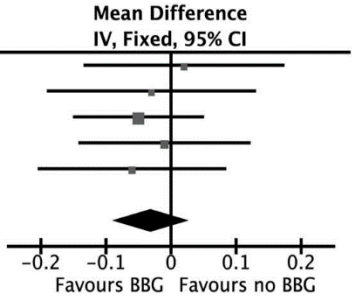
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 4 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = 0.24 (P = 0.81)



BBG vs no BBG (ICG/TB/TA/no dye)

	BBG			no BBG				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fukuda, 2011[18]	0.61	0.29	31	0.59	0.27	22	14.7%	0.02 [-0.13, 0.17]	
Baba, 2012[21]	0.79	0.33	35	0.82	0.31	28	13.5%	-0.03 [-0.19, 0.13]	
Williamson, 2013[23]	0.93	0.4	109	0.98	0.47	209	35.0%	-0.05 [-0.15, 0.05]	
Mochizuki, 2014[25]	0.86	0.22	15	0.87	0.31	82	20.1%	-0.01 [-0.14, 0.12]	
Machida, 2014[26]	0.63	0.22	16	0.69	0.27	32	16.7%	-0.06 [-0.20, 0.08]	
Total (95% CI)			**206**			**373**	**100.0%**	**-0.03 [-0.09, 0.03]**	

Heterogeneity: $Chi^2 = 0.83$, df = 4 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = 1.03 (P = 0.30)

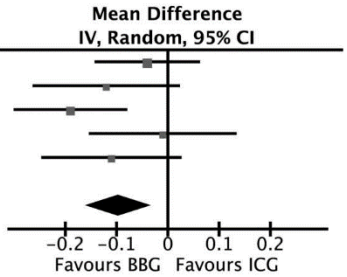


Visual Acuity

BBG vs ICG

	BBG			ICG				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fukuda, 2011[18]	0.1	0.2	31	0.14	0.17	22	26.2%	-0.04 [-0.14, 0.06]	
Baba, 2012[21]	0.25	0.3	35	0.37	0.27	28	16.3%	-0.12 [-0.26, 0.02]	
Williamson, 2013[23]	0.52	0.43	109	0.71	0.53	209	23.7%	-0.19 [-0.30, -0.08]	
Machida, 2014[26]	0.24	0.24	16	0.25	0.16	16	16.2%	-0.01 [-0.15, 0.13]	
Mochizuki, 2014[25]	0.33	0.2	15	0.44	0.35	61	17.6%	-0.11 [-0.24, 0.02]	
Total (95% CI)			**206**			**336**	**100.0%**	**-0.10 [-0.16, -0.03]**	

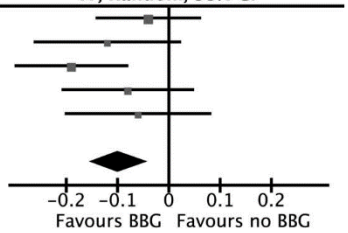
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.69$, df = 4 (P = 0.22); $I^2 = 30\%$
Test for overall effect: Z = 2.88 (P = 0.004)



BBG vs no BBG (ICG/TB/TA/no dye)

	BBG			no BBG				Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fukuda, 2011[18]	0.1	0.2	31	0.14	0.17	22	27.4%	-0.04 [-0.14, 0.06]	
Baba, 2012[21]	0.25	0.3	35	0.37	0.27	28	15.0%	-0.12 [-0.26, 0.02]	
Williamson, 2013[23]	0.52	0.43	109	0.71	0.53	209	24.1%	-0.19 [-0.30, -0.08]	
Mochizuki, 2014[25]	0.33	0.2	15	0.41	0.35	82	18.3%	-0.08 [-0.21, 0.05]	
Machida, 2014[26]	0.24	0.24	16	0.3	0.22	32	15.2%	-0.06 [-0.20, 0.08]	
Total (95% CI)			**206**			**373**	**100.0%**	**-0.10 [-0.16, -0.04]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.53$, df = 4 (P = 0.34); $I^2 = 12\%$
Test for overall effect: Z = 3.37 (P = 0.0007)



Author's Conclusion: …, there was no significant difference in anatomical outcome. Larger randomized and prospective studies with a longer duration of follow-up would be necessary to further confirm the usefulness of BBG for ILM peeling in patients with MH.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. Staining the internal limiting membrane is the claimed effect. The applicant has not claimed that there is improved visual acuity over other stains.

Study #2 Vital Dyes for Macular Surgery: A Comparative Electron Microscopy Study of the Internal Limiting Membrane[2]

Authors: Schumann RG, Gandorfer A, Priglinger SG, Kampik A, Haritoglou C,

Methods: A consecutive series of 96 patients who underwent vitrectomy in one eye with or without dye-assisted peeling of the ILM and epiretinal tissue during September 1998 and September 2007. 49 specimens of 49 eyes with idiopathic macular holes (IMH) and 47 specimens of 47 eyes with macular pucker (MP) were included. Specimens of ICG assisted macular surgery had been part of a previous investigation and were reassessed by obtaining new sections of these specimens. BBG sourced from Fluoron GmbH, Heu-Ulm, Germany.

Results: Ninety-six ILM specimens from 60 women and 36 men were included in this study, corresponding to 49 right eyes and 47 left eyes. The average age at time of surgery was 68 years (range: 48–85 years). Only one specimen per eye was analyzed. TB was used to stain the ILM in 30 eyes, corresponding to 15 eyes with IMH and 15 eyes with MP. BBG was used in 20 eyes: 14 eyes with IMH and 6 cases with MP. Bromphenol blue was used in 10 eyes: 2 eyes with IMH and 8 eyes with MP. Chicago blue was used in 6 eyes with MP, and ICG was used in 10 eyes: 6 eyes with IMH and 4 eyes with MP. As controls, 20 specimens without dye-assisted ILM peeling (12 eyes with IMH and 8 eyes with MP) were included in this series.

Analysis of the morphologic features of cellular and extracellular structures at the vitreal side of the ILM did not show any significant difference in the specimens removed with or without dye assistance in terms of cell and collagen distribution or cell and collagen type. If epiretinal fibrocellular proliferation was present, there were mostly single cells or cellular multilayers at the ILM.

Regarding the appearance of intracellular elements, there were no abnormalities in specimens after TB, BBG, BPB, and CB staining. All these specimens presented with well-preserved cellular and/or extracellular components such as cell nucleus, endoplasmatic reticulum, mitochondriae, intercellular junctions, and collagen fibrils of newly formed collagen, native vitreous collagen and fibrous long spacing collagen. In contrast, cellular proliferations at the

[2] **RETINA** 29:669–676, 2009

vitreal side of the ILM in specimens after ICG staining were not well preserved. Therefore, in these cases distinguished analysis of intra and extracellular structures was not possible.

In contrast to ILM specimens that were removed without dye assistance, more cellular debris at the retinal side of the ILM was seen after intravitreal dye administration in any case. This observation may indicate an interaction of the dye with components of the ILM affecting the rigidity of this delicate structure as described for the use of ICG as well. The structural evidence of retinal debris at the ILM can be used as an indicator for retinal damage. However, morphologic abnormalities alone do not provide conclusive insights in underlying pathomechanisms. The mechanism of dye-related retinal toxicity appears to be a multifactorial process and is still a subject of debate in experimental studies. Furthermore, it remains uncertain if the presence of retinal cell fragments at the ILM correlates with functional deficits.

Author's Conclusions: Trypan blue, BBG, BPB, and CB cause significantly less morphologic changes at the retinal cleavage plane than indocyanine green. Further studies are required to elucidate if presence and amount of retinal cell fragments at ILM specimens correlate with functional deficits.

Reviewer's Conclusion: Brilliant Blue G safely stains the internal limiting membrane. (b) (4)

Study #3: A Comparison of Brilliant Blue G, Trypan Blue, and Indocyanine Green Dyes to Assist Internal Limiting Membrane Peeling during Macular Hole Surgery[3]

Authors: Shukla D, Kalliath J, Meelakantan N, Naresh KB, Ramasamy K

Methods: Fifty eyes of 50 patients, 26 women and 24 men, were included in this nonrandomized comparative interventional case series between October 2006 and April 2008. The study was partly prospective, with two concurrent study groups (BBG and TB), and partly retrospective (ICG group). The inclusion criteria comprised senile idiopathic MHs, with visual symptoms solely attributed to MH, patients' willingness to follow-up for at least 6 months, and optical coherence tomography (OCT) documentation of a full-thickness MH. Both time domain and spectral-domain systems were used. Patients were examined on postoperative Day 1, Week 1, at Months 1, 3, and 6, and every sixth month thereafter. Data regarding postoperative complications, BCVA, closure of the MH by slit-lamp biomicroscopy, and by OCT were documented at each review visit. A complete closure of the inner retinal dehiscence determined by means of OCT was considered as a successful hole closure. Anatomical and functional results with the 3 dyes were compared at 6-month visit for this analysis. BBG sourced from Ocublue Plus: Aurolab.

Anatomical and Visual Outcomes

(BCVA/MH Closure)	Brilliant Blue (%)	Trypan Blue (%)	Indocyanine Green (%)	*P**
Improved	12 (80%)	17 (85%)	5 (33%)	0.010
20/40 or better	5 (33%)	6 (30%)	1 (7%)	0.197
Worsened	1 (7%)	1(5%)	6 (40%)	0.049
MH closure	15 (100%)	19 (95%)	13 (86%)	0.480

*All comparisons involved combined BBG + TB as a single group against the ICG group at the 6- month follow-up visit. ; TB, 0.15%; ICG, 0.5%.

Surgeon's Intraoperative Assessment of Facility of Dye Usage (1=satisfactory, 4=excellent)

	Indocyanine Green	Trypan Blue	Brilliant Blue
Ease of preparation	2	4	4
Staining intensity	4	2	3
Ease of Use	4	2	4
Ease of ILM peeling	4	2	4
Ease of dye removal	1	3	4

[3] **RETINA** 31:2021-2025, 2011

Author's Conclusion: Brilliant blue G was comparable with TB in optimizing visual and functional outcomes, while it was similar to ICG in ease of internal limiting membrane peeling.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. This study is suggestive of a better outcome in terms of visual acuity than indocyanine green, however, the indocyanine green arm was not concurrently controlled. The study is supportive of safety of the drug substance since the concentration was twice that proposed by the applicant.

Study #4: Internal limiting membrane staining (2012)[4]

Authors: Caramoy A, Kirchhof B, Hahn M, Schroeder S, Fauser S, Muether PS

Design: Randomized, single-center, 2-arm clinical trial evaluating the functional outcomes of Green (ICG) or Brilliant Blue G (BB). 56 eyes with macular hole (n=28) or macular pucker (n=28). Patients were randomly assigned either to ICG- or BB-assisted macular ILM peeling, with additional epiretinal membrane peeling in pucker cases. BBG sourced from Fluoron GmbH, Ulm, Germany.

One-year outcome data were available for 23 macular hole patients (88%; ICG=12; BB=11) and 21 pucker patients (84%; ICG=13; BB=8).

Macular hole logMAR	Brilliant Blue	Indocyanine Green	
Baseline VA	0.55 ± 0.10	0.50 ± 0.08	No significant difference
Final VA	0.31 ± 0.15	0.30 ± 0.13	No significant difference
Baseline Reading BCVA	0.71 ± 0.21	0.68 ± 0.18	No significant difference
Final Reading BCVA	0.40 ± 0.17	0.48 ± 0.18	No significant difference

Macular Pucker logMAR	Baseline	Final	
Brilliant Blue	0.34 ±0.17	0.20 ± 0.10	0.034
Indocyanine Green	0.26 ± 0.19	0.21	0.39

For macular pucker, only distant BCVA in the BB group improved (from 0.34±0.17 to 0.20±0.10, *P*=0.034). Distant BCVA did not improve in the macular pucker ICG group. Reading VA did not improve in both macular pucker groups.

[4] **Ophthalmology** 119(6):1282, June 2012

Author's Conclusion: The key shortcoming of this study was the relatively small patient number. (b) (4)

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. There was no significant difference between groups in terms of visual acuity. The study is supportive of the application because the same drug substance was used in the same concentration as proposed in this application.

Study #5: Idiopathic macular hole: analysis of visual outcomes and the use of indocyanine green or Brilliant Blue G for internal limiting membrane peel (2014)[5]

Authors: Williamson TH and Lee E

Methods: Baseline, surgical, and outcome data for 351 consecutive primary macular hole surgeries was prospectively collected using electronic medical record software between 2001 and 2011. The outcomes for these cases were analyzed in relation to staging and the use of Indocyanine Green (ICG) (0.5 mg/ml) or Brilliant Blue G (BB) for ILM peel. Source of dye not stated.

Results: Mean age was 68.9 years (range 39–87) with 66% females and 54% right eyes. Follow-up duration was median 0.55 years.

	Brilliant Blue (n=109)	Indocyanine Green (n=209)	
Baseline VA - LogMAR	0.93	0.98	
Postop VA LogMAR	0.52	0.71	p=0.003
Macular hole closed	40%	26%	p=0.02

Author's Conclusions: Macular hole stage is a useful measure to help predict the chance of postoperative hole closure and visual outcome. The relationship between duration of symptoms and increasing stage suggests macular hole patients require prompt referral for consideration of early surgery. Better visual outcomes were achieved with Brilliant Blue G for ILM peel than with ICG.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. This study is suggestive of a better outcome in terms of visual acuity. The source

[5] **Graefes Arch Clin Exp Ophthalmol** 252:395-400, 2014

of the drug product is not stated and therefore not known, but may have been the applicant's product.

Study #6: Comparison of Vitrectomy with Brilliant Blue G or Indocyanine Green on Retinal Microstructure and Function of Eyes with Macular Hole (2012)[6]

Authors: Baba T, Hagiwara M, Sato E, Arai M, Oshitari T, Yamamoto S

Design: Comparative, retrospective, interventional case series

Participants: 63 eyes of 63 consecutive cases with macular holes (MH) were studied. 35 eyes of 35 cases were treated with Brilliant Blue G between January and August 2011. 28 eyes of 28 MH cases were treated with ICG from April 2009 through April 2010.

Methods: Vitrectomy was performed with a 23-gauge system and 0.25 mg/ml Brilliant Blue G or with 0.125% ICG. BBG sourced from the applicant, DORC, Zuidland, Netherlands.

Outcome Measures: The best-corrected visual acuity (BCVA) and the microperimetry determined retinal sensitivity were measured at baseline and at 3 and 6 months after surgery. The length of the defect of the photoreceptor inner segment/outer segment (IS/OS) junction and external limiting membrane (ELM), the central foveal thickness (CFT), and the thickness of the ganglion cell complex (GCC) were measured in the spectral domain optical coherence tomographic images.

Results: There were no statistically significant differences between groups in baseline characteristics.

Best corrected visual acuity (logMAR)	Brilliant Blue	Indocyanine Green	p value
Preop BCVA	0 .79 ± 0.33	0.82 ± 0.31	0.63
3 months	0.38 ± 0.31	0.49 ± 0.28	0.021
6 months	0.25 ± 0.30	0.37 ± 0.27	0.045

Retinal Sensitivity in Central 2 degrees	Brilliant Blue	Indocyanine Green	p value
Preop	8.2 ± 3.6	7.8 ± 4.1	0.73
3 months	14.3 ± 3.01	11.4 ± 3.4	0.001
6 months	14.5 ± 3.20	12.6 ± 3.6	0.03

Author's Conclusions: … the morphologic features of the inner and outer retina were studied by SD-OCT and the function was studied by the BCVA and retinal sensitivity in eyes after

[6] **Ophthalmology** 119:2609–2615, 2012

MH surgery using BBG and ICG for ILM peeling. The postoperative BCVA and central retinal sensitivity were better in eyes after BBG-assisted vitrectomy. The restoration of IS/OS junction was faster in BBG group, but the ELM defect and GCC thickness were not different in eyes with BBG and ICG. The CFT was associated with the restoration of IS/OS and ELM and recovered better in eyes that underwent BBG-assisted vitrectomy. Based on these findings, BBG may be a better agent than ICG to make the ILM more visible.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. This study is suggestive of a better outcome in terms of visual acuity and retinal sensitivity. The study used the to be marketed product.

Study #7: Internal Limiting Membrane contrast after Staining with Indocyanine Green and Brilliant Blue G during Macular Surgery (2013)[7]

Authors: Kadonosono K, Arakawa A, Inoue M, Yamane S, Uchio E, Yamakawa T, Taguiri M, Morit S, Ridgeley JR, Yanagi Y

Purpose: To evaluate the difference in color contrast by performing a color contrast ratio (CR) analysis and resulting visibility of the internal limiting membrane (ILM) when stained with indocyanine green and Brilliant Blue G during macular surgery by performing a color CR analysis.

Methods: The authors analyzed 40 consecutive cases in which vitrectomy with ILM removal was performed to treat a macular hole or an epiretinal membrane. The surgical procedure was performed in 21 patients (21 eyes) after staining with indocyanine green and in 19 patients (19 eyes) after staining with Brilliant Blue G. The color CRs were estimated based on digital analysis of the red, green, and blue data of the digital images captured, and the CRs obtained with the two dyes were compared. This paper used BBG sourced from Sigma-Aldrich, St. Louis, MO. (b) (4).

Results: Color contrast analysis was performed in all 40 eyes, in which the ILM was removed after staining with indocyanine green or Brilliant Blue G, and the CRs were estimated in every eye.

The color Contrast Ratio (CR) was calculated using the following formula: Color CR = (Lmax +0.05) / (Lmin + 0.05), where Lmax – luminance of the brighter background and Lmin = luminance of the darker background.

BCVA (logMAR)	Brilliant Blue	Indocyanine Green	p value
Preoperative	0.52 ± 0.4	0.60 ± 0.3	0.44
3 months	0.31 ± 0.2	0.32 ± 0.1	0.31

[7] **RETINA** 33:812-817, 2013

6 months	0.18 ± 0.1	0.18 ± 0.3	0.83

Contrast Ratio	Brilliant Blue	Indocyanine Green	p value
	4.3 ± 0.3	2.4 ± 0.1	0.15

Author's Conclusion: …, the results of this study showed that the color contrast of the ILM varied with the dye used, and digital color contrast analysis can be used to evaluate the visibility of digital images, and it may be useful when choosing the dye to use for staining the ILM better.

Reviewer's Conclusions: Agree with Author's conclusion. (b) (4)

Study #8 Comparative evaluation of anatomical and functional outcomes using brilliant blue G versus triamcinolone assisted ILM peeling in macular hole surgery in Indian population.[8]

Authors: Kumar A, Gogia V, Shah VM, Nag TC.

Methods: A retrospective, comparative, non-randomized, single center, interventional study was performed, in a series of macular hole surgeries done during the period May 2008 to May 2009, performed by a single surgeon (author) with at least 1 year follow-up. The drug product was sourced from Ocublue Plus, Aurolab, Aravind Eye Care System, Madurai, India

Results: Anatomical hole closure was achieved in 85 eyes (90.43%) and visual gain in 78 eyes (82.9%). Mean postoperative follow-up duration was 16.14±1.95 months. No significant difference was found in anatomical and functional success between the two groups. Triamcinolone had a significantly higher incidence of postoperative glaucoma. Duration of symptoms of <12 months (p=0.004) and preoperative visual acuity ≤1.0 LogMAR were related to anatomical success. However, greater visual gain was found in patients with chronic holes (≥12 months) (p=0.046) and poor preoperative visual acuity (>1.0 LogMAR) (p=0.001).

Author' Conclusion: Conclusion BBG-assisted ILM peeling offers an effective alternative to triamcinolone, with the added advantage of marked enhancement of vitreoretinal interface contrast with comparable hole closure rates and visual outcomes.

Reviewer's Comments: No significant safety concerns were identified. The drug product used in this trial was twice the concentration proposed in this application.

[8] **Graefes Arch Clin Ophthalmol.** 249:987-995, 2011

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Study #9: Long-term outcomes of 3 surgical adjuvant used for internal limiting membrane peeling in idiopathic macular hole surgery.[9]

Authors: Mochizuki N, Yamamoto T, Enaida H, Ishibashi T, Yamashita H.

This was a retrospective cohort study involving 97 eyes of 94 patients who underwent vitreous surgery for idiopathic MH and were followed up for over 3 months at Yamagata University Hospital between June 2002 and November 2010. The patients comprised 48 men (49 affected eyes) and 46 women (48 affected eyes). They were divided into 3 groups according to the dye used for ILM peeling: the BBG group (15 eyes), the ICG group (61 eyes), and the TA group (21 eyes). No significant differences were detected between any 2 of these 3 groups in terms of the male-to female ratio, age, MH stage (2 to 4) distribution, or visual acuity. The MH was significantly larger in the BBG group than in the other 2 groups. The proportion of phakic eyes before surgery was significantly lower in the BBG group than in the other 2 groups. Source of BBG was not identified.

logMAR VA	Brilliant Blue	Indocyanine Green	Triamcinolone
Pre-op	0.86 ± 0.22	0.84 ± 0.31	0.94 ± 0.30
3 months	0.40 ± 0.25	0.59 ± 0.36	0.44 ± 0.34
6 months	0.37 ± 0.20	0.57 ± 0.36	0.41 ± 0.37
1 year	0.33 ± 0.20	0.44 ± 0.35	0.33 ± 0.34
1.5 years	0.21 ± 0.18	0.37 ± 0.30	0.30 ± 0.29
2 years	0.16 ± 0.14	0.35 ± 0.28	0.28 ± 0.30

The initial closure rate was 86.7 % (n = 15) in the BBG group, 86.9 % (n = 61) in the ICG group, and 90.5 % (n = 21) in the TA group; no significant intergroup difference was detected (Fisher exact test, P = 1.00).

Authors Conclusions: This was a retrospective study. Some factors in the patients' backgrounds differed among the 3 adjuvant groups. Our sample size was also relatively limited. Despite these limitations, to the best of our knowledge, this study has demonstrated for the first time that BBG provides a safe modality for staining the ILM and that the intensity of the chromatic response to BBG was not inferior to that of the other 2 dyes. We may therefore conclude that BBG is useful as an adjuvant during ILM peeling.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. This study is suggestive of a better outcome in terms of visual acuity. The source of the drug product was not identified in the published article. The source may have been the applicant's marketed product.

[9] **Jpn J Ophthalmol** 58:455-461, 2014

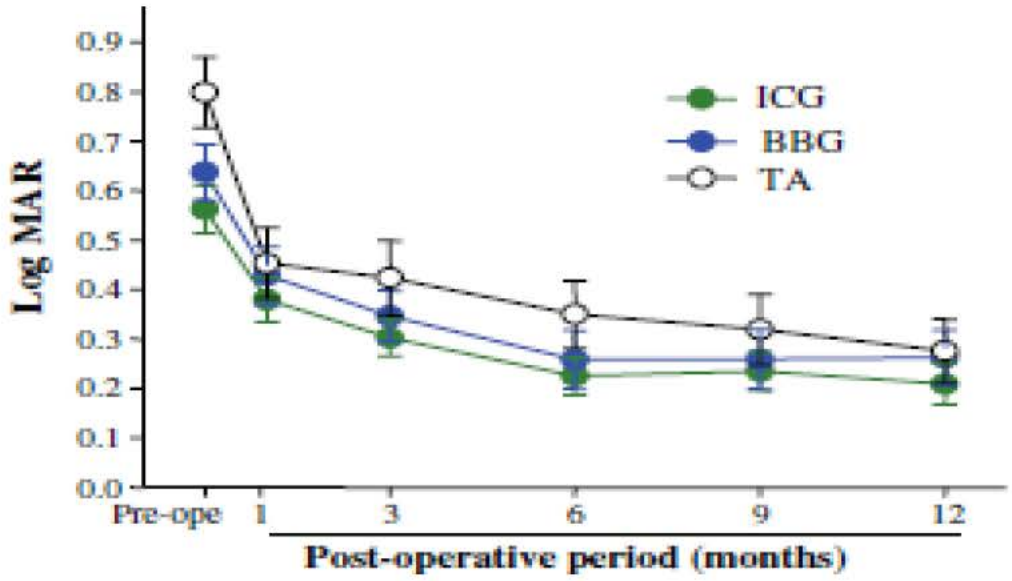
Study #10: Comparisons of cone electroretinograms after indocyanine green-, brilliant blue G-, or triamcinolone acetonide-assisted macular hole surgery[10]

Authors: Machida S, Toba Y, Nishimura T, Ohzeki T, Murai K, Kurosaka D.

Methods: 51 eyes of 51 consecutive patients who underwent vitrectomy with ILM peeling during MH surgery from January 2011 to July 2012. All patients did not have any ocular disease other than a MH and cataract. Three patients were excluded because the intraocular pressure was > 30 mmHg postoperatively. The remaining 48 patients consisted of 32 women and 16 men whose mean age was 64.6 ±7.62 (mean ±standard deviation) years with a range from 47 to 76 years. Because nuclear cataracts commonly develop after vitrectomy in patients older than 50 years, all patients underwent vitrectomy combined with phacoemulcification and aspiration (PEA) with implantation of an intraocular lens (NX-70, Advanced Vision Science, Inc., Coleta, CA, USA). (b) (4)

Results: Each patient was randomly assigned to either the IGG (n=16), BBG (n=16) or TA (n=16) group. The average operation time was 41.8±6.90 min (mean±SD) for ICG, 40.6±5.86 min for BBG, and 37.1±6.57 min for TA. The differences in the surgical times were not significant.

The BCVAs in logarithm of the minimum angle resolution (logMAR) units before and after surgery are shown below.



[10] Graefes Arch Clin Exp Ophthalmol. 252:1423-1433, 2014

There were no significant differences in the BCVA among the ICG, BBG, and TA groups at each postoperative time. Changes between the baseline and final BCVA were 0.373±0.193 logMAR units (mean±SD), 0.382±0.166 logMAR units, and 0.528±0.241 logMAR units for the ICG, BBG and TA groups, respectively. The differences among the groups were not significant (P=0.082). The differences in the visual sensitivities, represented by the MDs, were not significant at the different preoperative and postoperative times among the ICG, BBG, and TA groups.

Author's Conclusions: Although there were no significant differences in the BCVA and sensitivities (SAP), the PhNR amplitude was reduced in the ICG and BBG groups postoperatively. A complete recovery of the PhNR amplitude was seen in the BBG group, while the PhNR amplitude did not return to the preoperative level in the ICG group, even at 12 months after surgery. This indicates that the PhNR may detect subclinical impairment of RGCs caused by the possible toxic effects of ICG. This finding adds to the data that BBG and TA may be safer than ICG for use during MH surgery.

Reviewer's Conclusion: Brilliant Blue G safely and effectively stains the internal limiting membrane. There was no significant difference between groups in terms of visual acuity. (b) (4)

Study #11 Residual Internal Limiting Membrane after Epiretinal Membrane Peeling.[11]

Authors: Carpentier C, Zanolli M, Wu L, Sepulveda G, Berrocal MH, Saravia M, Diaz-Llopis M, Gallego-Pinazo R, Filsecker L, Verdaguer-Diaz J, Milan-Navarro R, Arevalo JF, Maia M.

Methods: A prospective, multicenter, observational study of 98 eyes undergoing pars plana vitrectomy and membrane peeling for idiopathic ERM. All eyes underwent core vitrectomy (20, 23, or 25 gauge) followed by intravitreal triamcinolone to verify that the posterior hyaloid had been removed. Brilliant blue G (0.2 mL of 0.25 mg/mL) was injected into the vitreous cavity and washed out immediately. The ERM was peeled and then the surgeon observed and recorded the characteristics of the underlying ILM. The posterior pole was restained with brilliant blue G (0.2 mL of 0.25 mg/mL), and the same observations on the characteristics of the ILM were recorded. Peeling of the remaining ILM was performed. The main outcome measured was the status of the ILM after ERM peel. Secondary outcomes included best-corrected visual acuity and central macular thickness at 6 months postoperatively. BBG was sourced from this applicant, DORC, as well as from Ophthalmos, Sao Paulo Brazil and Fluoron, Germany.

[11] RETINA 33:3026-2031, 2013

Results: After ERM peel, all of the eyes had residual ILM. In 74 eyes, the ILM was present and damaged, whereas in 24 eyes, the ILM was present and undamaged. In 37 eyes, the operating surgeon was unable to determine the status of the ILM before brilliant blue G staining. At 6 months, the logarithm of the minimum angle of resolution best-corrected visual acuity improved from 0.75 ± 0.39 at baseline to 0.31 ± 0.26 (P , 0.0001). The central macular thickness also improved from 460 ± 91 mm at baseline to 297 ± 102 mm (P , 0.003).

Author's Conclusion: Internal limiting membrane is frequently still present after ERM peeling. Staining with brilliant blue G facilitates its identification.

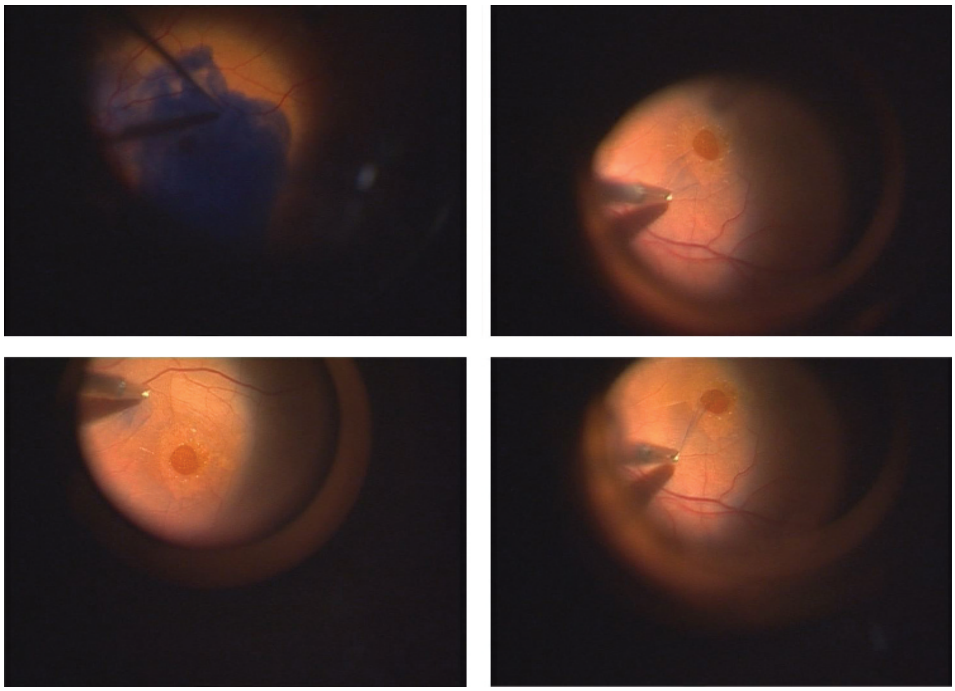
Reviewer's Conclusion: Brilliant Blue G was safe after repeated staining. The applicant's proposed drug product was one of the products used in this clinical trial.

Study #12 An in vivo evaluation of Brilliant Blue G in animals and humans.[12]

Remy M, Thaler S, Schumann RG, May CA, Fiedorowicz M, Schuettauf F, Gruterich M, Priglinger SG, Nentwich MM, Kampik A, and Haritoglou C

The following graphic depicts an *in vivo* evaluation of Brilliant Blue G in a patient with a traumatic macular hole, which appeared in a 2008 published article of the British Journal of Ophthalmology. The graphic illustrates administration of Brilliant Blue dye, selective staining of the internal limiting membrane and subsequent removal of the stained internal limiting membrane leaving the unstained retinal tissue in place.

[12] **Br J Ophthalmol.** 92:1142–1147, 2008



Efficacy Summary Statement

The published literature support that the internal limiting membrane can be adequately visualized with TissueBlue 0.025%. Improved visualization can be expected to improve the safety of the surgical procedure

9. Safety

From the original Medical Officer Review dated 10/3/2019:

Safety Database

Post-marketing experience including more than (b) (4) units of Brilliant Blue G 0.025% Solution marketed outside of the United States is favorable, with no reports of adverse events related to the drug product having been reported. (b) (4) .

Based upon a review of the literature by the applicant:
The total number of subjects in the safety population was 2,627 comprising 2,645 eyes. A total of 284 adverse events were reported across all treatment groups, 133 of which were within BBG treated subjects. AE's reported following the use of BBG were reported in 12% of subjects (133 of 1,159). Adverse events observed in BBG treated subjects such as retinal tear, retinal hemorrhage, and cataract formation or progression are commonly attributed to vitrectomy procedures.

The most commonly reported AE for subjects treated with BBG (N=69 reporting AE within this treatment type) was cataract development or progression, occurring in 6% of subjects. Vitreous detachment, transient ocular hypertension and retinal hemorrhage also occurred in approximately 1% of subjects. All reported AEs are common to the ophthalmic surgical procedures that were performed and are unlikely to be caused by the dye.

There were no serious adverse events or deaths reported. No differences in population subgroups including age or race have been identified. No long-term or delayed adverse events have been reported.

The mean number of intravitreal injections was similar for each treatment group.

Safety Summary Statement

The published literature and the post-marketing experience from Eurpoe support that TissueBlue 0.025% has a relatively safe profile. Adverse reactions that have been reported in procedures that included the use of TissueBlue 0.025% have beenoften been associated with the surgical procedure. and not the drug. The complications include retinal (retinal break, tear, hemorrhage, and detachment) and cataract complications.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

11. Pediatrics

This product has an orphan drug designation. The safety and effectiveness of TissueBlue 0.025% in pediatric patients has not been established.

12. Other Relevant Regulatory Issues

BIOSTATISTICS
This is a 505(b)(2) application relying on published literature. The applicant has not conducted any clinical studies; however, clinical studies using this particular product have been conducted by individual clinicians and published. Biostatitics did not perform a review of this application.

FINANCIAL DISCLOSURE
The applicant did not sponsor any clinical studies. The clinical data supporting the safety and efficacy of the drug product is derived from the published literature. There are no "Covered" studies.

OSI
The applicant did not sponsor any clinical studies. The clinical data supporting the safety and efficacy of the drug product is derived from the published literature. There are no "Covered" studies. An Office of Scientific Investigations (OSI) audit was not requested.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, TissueBlue, and granted conditional acceptance on 8/2/2019. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a labeling review of the originally submitted USPI and carton/container labeling on 10/11/2019.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete labeling on 11/19/2019.

DRISK
The Division of Risk Management (DRISK) completed a reviw dated 10/29/2019. The benefit-risk profile is favorable; therefore, a REMS is not necessary for this product to ensure that the benefits outweigh the risks.

13. Regulatory Action

NDA 209569 TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% will be approved for use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

The following post-marketing commitments, agreed to by the applicant, will be included in the approval letter. An expiration date of 12 months is granted when stored at 15 °C- 25 °C.

1. Post Marketing Commitment # 3724-1: Provide 12-month stability update for Batch 14218 and 6-month stability data for Batch 21618. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

2. Post Marketing Commitment # 3724-2: Any further extension of the expiration date post-approval will need to be submitted for review as a PAS supplement. Final protocol submission date: May 15, 2020; study completion: April 15, 2021; and final report submission: May 15, 2021.

3. Post Marketing Commitment # 3724-3: A leachable study on at least one stability Batch 14618 should be conducted through its expiration date. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

4. Post Marketing Commitment # 3724-4: Develop a consistently readable barcode on the Tyvek blister for the TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% product. Final report submission: December 31, 2020.

14. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

√	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	√	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		√	Clinician reported outcome (ClinRO)	Section 8 and 9 this review; Module 5 of application
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

15. Labeling

The labeling that will be approved for NDA 209569 TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% indicated to selectively stain the internal limiting membrane is included below.

8 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
12/17/2019 01:12:54 PM

WILEY A CHAMBERS
12/17/2019 10:54:04 PM

PETER P STEIN
12/20/2019 07:42:06 AM