MEDDOCS Open Access Publisher

Annals of Ophthalmology and Visual Sciences

Open Access | Research Article

Agreement between Investigator and Central Reading Center Gradings of Meibomian Secretion Quality in Participants with and without Meibomian Gland Dysfunction: A Pilot Study

Isabella Tunon-Robinson[1]; Nay Akeh[2]; Ashley Nguyen[3]*; Cathy Zhao[3]; Xiaoming Xu[3]; Kelly K Nichols[4]

[1]Arizona State University, School of Computing and Augmented Intelligence, Tempe, AZ, USA.

[2]University of Southern California, Los Angeles, CA, USA.

[3]Allergan, an AbbVie company, Irvine, CA, USA.

[4]School of Optometry, University of Alabama at Birmingham, Birmingham, AL, USA.

***Corresponding Authors: Ashley Nguyen**

Allergan, an AbbVie company, Irvine, CA, USA.
Tel: 714-246-5910; Email: anguyen@abbvie.com

Received: Oct 09, 2024

Accepted: Nov 04, 2024

Published Online: Nov 11, 2024

Journal: Annals of Ophthalmology and Visual Sciences

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Central reading center; Meibomian gland dysfunction; Meibum secretion quality grading.

Abstract

Objective: Meibomian Gland Dysfunction (MGD) is commonly associated with dry eye disease. Central Reading Centers (CRC) can provide standardized grading reducing bias and variability across clinical sites. The objective of this study was to compare investigator grading of meibomian gland secretion quality in participants with and without MGD to grading performed by a CRC.

Methods: This clinical study classified participants into non-MGD, mild/moderate MGD, and severe MGD cohorts. Meibum secretions were expressed from the lower lid and graded by the investigator. A video was recorded concurrently and sent to a CRC. The Maximum Meibum Quality Score (MMQS) was calculated. A Gwet's AC1 agreement coefficient was used to evaluate agreement in MMQS as either normal (0 or 1) or abnormal (2 or 3) between the investigator and CRC.

Results: 75 participants were enrolled in 3 cohorts. The agreement score between investigator-assessed and CRC-assessed MMQS in the study eye at day 1 was Fair (0.26), Substantial (0.72) and Substantial (0.80) for the non-MGD, mild/moderate MGD, and severe MGD cohorts, respectively.

Conclusions: There was a substantial level of agreement between investigator and CRC-assessed MMQS scores in cohorts with MGD; however, there was only fair agreement in participants without MGD. This may be due to meibum secretions that are often optically clear in people without MGD impacting the accuracy of grading from a video image. Results suggest investigative sites using high-quality imaging may lead to more accurate assessments at the CRC, and should be considered for future clinical studies in participants with MGD.

Cite this article: Tunon-Robinson I, Akeh N, Nguyen A, Zhao C, Xu X, et al. Agreement between Investigator and Central Reading Center Gradings of Meibomian Secretion Quality in Participants with and without Meibomian Gland Dysfunction: A Pilot Study. Ann Ophthalmol Vis Sci. 2024; 7(2): 1046.

Introduction

Dry Eye Disease (DED), generally, can be categorized as aqueous deficient, evaporative, or mixed mechanisms as defined by the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop II (DEWS-II) [1]. Aqueous deficiency arises from reduced lacrimal gland production, and evaporative disease arises from abnormalities in the tear film lipid layer. Meibomian Gland Dysfunction (MGD) is a major cause of disruption of the tear film lipid layer and consequently of DED [2]. In a meta-analysis, the prevalence of MGD was 21.2% in studies published since 2010 in the United States [3]. A study conducted by DED experts demonstrated that 86% of patients with DED had evidence of MGD [4]. A high percentage of patients with DED and MGD have symptoms that are not resolved using marketed topical immunomodulators, as a result, a large number of patients discontinue therapy after a few months [5]. Thermopulsation devices warm and massage the lids to improve meibum flow but do not necessarily address the underlying cause of MGD so meibomian gland loss persists and repeat therapies are frequently required [6].

Given the unmet needs in treatments available to effectively treat MGD, there are numerous clinical trials that have been conducted, or are in progress, to treat MGD. As of May 9, 2024, there were 168 registered clinical trials on ClinicalTrials.gov with the condition/disease listed as MGD, many of which are evaluating investigational pharmaceutical eye drops or devices and meibum secretion quality is being used as an outcome measure [7]. Given the interest in using meibum secretion quality as an outcome measure in multicenter clinical trials, we conducted a clinical study to compare investigator grading of meibomian gland secretion quality in participants with and without MGD with grading performed by a Central Reading Center (CRC). Although Investigator grading of the quality of meibum secretions is the gold standard, the use of CRCs for meibum secretion grading has not been previously reported. Nevertheless, the use of CRCs has become commonplace in eye related studies and can provide standardized grading and data analysis, thus reducing bias and variability across clinical sites [8].

We conducted a clinical trial and previously reported on participants with no MGD, mild/moderate MGD and severe MGD that explored the signs and symptoms of MGD that can be used as efficacy endpoints [9], patient reported outcomes questionnaires [10], and meibum collection and biochemical analysis [11]. Herein, we report the results comparing investigator grading of meibomian gland secretion quality with grading performed by a CRC in participants with and without MGD.

Material and Methods

This prospective, multicenter, noninterventional clinical study was conducted in accordance with the Declaration of Helsinki and applicable regulations. An institutional review board or ethics committee reviewed and approved the study protocol and all participants provided written informed consent before screening. The study was registered at ClinicalTrials.gov with the identifier NCT01979887. Three sites were selected for this clinical trial (2 sites in the United States, 1 site in the United Kingdom), and the Principal Investigators at each site were licensed optometrists with PhD degrees (2) and a US board-certified ophthalmologist (1). All were recognized dry eye experts and had participated previously in numerous clinical trials with DED participants.

Participant Selection and Assignment to Cohorts

Selection criteria used for cohort assignment into non-MGD, mild/moderate MGD, and severe MGD were consistent with diagnostic criteria and severity grading established by the TFOS International Workshop on Meibomian Gland Dysfunction[12,13]. A composite grading scale was based on the investigator-graded MMQS, the sum of scores for the worst 2 symptoms on an ocular symptom questionnaire, and Schirmer test results (Table 1). A subject's meibomian gland secretions from the 6 central glands of the lower lids were evaluated at enrollment Day 1 by the investigator using a Meibomian Gland Evaluator™ (Johnson and Johnson, Irvine, CA, USA). This device was developed specifically for applying a standardized amount of pressure to the lower lid to express lipid from the meibomian glands. The Maximum Meibum Quality Score (MMQS) was defined as the maximum score among expressible glands (graded as 0, 1, 2, 3), as assessed by the investigator based on Mathers' meibum quality secretion grading scale [14]:

0 Clear excreta or clear with small particles (normal viscosity).

1 Opaque excreta with normal viscosity.

2 Opaque excreta with increased viscosity (gel-like).

3 Secretions retain shape (or secretions do not completely express but a toothpaste-like substance can be seen at the opening of the orifice).

NE non-expressible (nothing at orifice).

To be assigned to a cohort, at least one eye was required to meet the specified criteria for the cohort, and this eye (or the right eye if both eyes met the criteria) was designated as the study eye. The intent was to enroll 75 subjects (25 subjects per study cohort) who satisfied the cohort criteria.

Key inclusion criteria at baseline were

- Male or female, 40 years of age or older prior to the enrollment visit.

Key exclusion criteria at baseline were

- Subjects who had undergone LipiFlow® or other lid heating therapy, therapeutic gland expression, or meibomian gland probing within 12 months prior to the enrollment visit or anticipated use of such procedures during the study.
- Subjects who had worn a contact lens in either eye within 30 days prior to the enrollment visit or anticipated wearing a contact lens in either eye during the study.
- Subjects who had performed lid hygiene within 48 hours prior to the enrollment visit.
- Subjects who wore eye makeup within 8 hours prior to the enrollment visit.
- Subjects who used LATISSE or other eyelash growth-stimulating products within 30 days prior to the enrollment visit or anticipated use during the study.
- Subjects who used systemic or topical macrolides, tetracyclines or tetracycline derivative drugs (including doxycycline and minocycline) within 30 days prior to the enrollment visit or anticipated use during the study.

- Subjects who used any preserved topical artificial tear supplement (e.g., solutions, gels, ointments) within 30 days prior to the enrollment visit or anticipate used during the study.
- Subjects who used any non-preserved artificial tear supplement (e.g., solutions, gels, ointments) within 6 hours prior to the enrollment visit.
- Subjects who used systemic antihistamines within 30 days prior to the enrollment visit or anticipate used during the study.

Study participants who met the enrollment criteria were assigned to a study cohort: non-MGD, mild/moderate MGD, or severe MGD. Each site had a video camera mounted on a slit-lamp and a recording was performed concurrent with the meibum expression of the subject's lower lid of each eye. A single investigator at each site would grade the meibum secretions while pressing on the lower lid with the Meibomian Gland Evaluator™. The video recordings took approximately 2 minutes per eye and they were sent to the CRC for evaluation. The meibum secretion observed on the video recording was evaluated during the pressure on the lower eyelid to be able to determine the degree of clarity and viscosity of the meibum which were critical attributes in determining the meibum quality secretion grade. Since this was a pilot study, and the first to establish a CRC for meibum quality assessment, a single central reader with 20+ years of experience in evaluating DED outcome measures including meibum secretion quality, evaluated all the video recordings from each site.

Methods

As discussed above, the Composite Grading Scale for MGD Severity is based on MMQS, Schirmers, and Symptoms (Table 1). The required investigator graded MMQS that defines normal on the Composite Grading Scale is a 0 or 1 and abnormal (i.e. mild/moderate or severe MGD) has an MMQS of a 2 or 3. A Gwet's AC1 agreement coefficient [15] was used to evaluate agreement in MMQS, either normal (0 or 1) or abnormal (2 or 3), between investigator and CRC. In this study, the observed data exhibited the extreme marginal distribution where Cohen's kappa may produce misleading results. Gwet's AC1 can overcome this limitation and was considered a more reliable agreement analysis method for this study. Figures 1A and 1B are examples of normal and abnormal meibum secretions, respectively. The following benchmark scale was used to assess the degree of agreement: < 0 No; 0.00 to 0.20 Slight; 0.21 to 0.40 Fair; 0.41 to 0.60 Moderate; 0.61 to 0.80 Substantial; 0.81 to 0.99 Near Perfect; 1.00 Perfect.

Results

A total of 75 subjects (25 per cohort) qualified for, and were placed into, the non-MGD, mild-to-moderate MGD, and severe MGD cohorts (Table 2). Most enrolled subjects were women, which is typical in DED studies, and given the relatively small sample size of this study, enrollment into the 3 cohorts was reasonable balanced with respect to age and sex. There were imbalances between cohorts with respect to race. In the non-MGD cohort, the majority of subjects were Caucasian; in the mild/moderate MGD cohort, the majority were Black/African American; and in the severe MGD cohort, the majority were Black/African American and Hispanic/Latino via self-report. The Gwet's AC1 score evaluating the agreement with investigator-assessed and CRC-assessed MMQS in the study eye at Day 1 was 0.26 (Fair), 0.72 (Substantial) and 0.80 (Substantial) for the 3 cohorts, non-MGD, mild/moderate MGD, and severe MGD, respectively (Table 3).

Discussion

MGD is commonly associated with DED and numerous clinical trials are being conducted to approve therapies to treat this condition. Some topical therapies may penetrate into the meibomian glands [16] and potentially be disease modifying by improving the quality of the meibum secretions and this has been explored in randomized clinical trials [17]. To aid in providing reproducible data with evaluating the quality of the meibum, the Meibomian Gland Evaluator™ was developed that applies reproducible force on the eyelid margin to express lipid from the meibomian glands [18]. This device was deployed in our study at all sites and helps reduce the noise across sites if they were applying variable amounts of digital pressure on the lid margin to express meibum. Although the use of a CRC to assess the meibum quality during expression has not been previously reported, we hope to add to the standardization of procedures so that future MGD studies can use similar methods. The CRC will assist in reducing the variability in meibum secretion quality grading across sites. It is difficult to compare results across studies with MGD participants when different methods of meibum expression are used and different scales have been employed to grade the meibum quality. As a result, we used the Mathers' grading scale for meibum quality assessment that has been commonly used in previous clinical studies [13]. In addition, we employed the previously used MMQS to distill the meibum quality per eyelid down to single number. Participants were classified into categories of non-MGD, mild/moderate MGD, and severe MGD based on a composite suggested by the TFOS International Workshop on Meibomian Gland Dysfunction, which were composed of a group of international subject matter experts that reviewed the current practice patterns and published evidence on MGD [12,13]. In our pilot study, there was substantial level of agreement between investigator and CRC-assessed MMQS scores in cohorts with MGD, however, there was only fair agreement in participants without MGD. Post-hoc, we examined the root cause of the discrepancy between the investigator and CRC grading in participants with non-MGD, and it was evident that the meibum secretions were graded more severely by the CRC. In this non-MGD category, approximately half the participants assessed by the CRC were a grade 2 or 3, had been classified by the investigator as a 0 or 1. We investigated why a number of non-MGD participants were graded as more severe, compared with investigators that visualized normal meibum, and we noted that some participants on the video did not show any flow of meibum, but there was meibomian ostia prolapse that mimicked cloudy and pasty secretions. A good example is in Figure 1C where a participant had 5 of 6 glands graded as a 0, and the CRC read 6 of 6 graded as a 3. Notable is meibomian ostia prolapse or 'pouting' at the orifice that resembled pasty secretions emanating from the meibomian orifice. Grade 0 and 1 in some cases are optically clear and more prevalent in the non-MGD category impacting the accuracy of the meibum score grading from a video image. The learnings from our pilot study for future clinical trials included having investigative sites using higher-quality video imaging to lead to more accurate assessments at the CRC and also be observant that meibomian ostia prolapse may mimic more advanced grading of the meibum secretions. CRCs have an important role in the conduct of clinical trials, especially those related to eye care since image acquisition is commonly required. CRCs provide inputs on the study design, preparation of the operations manual, and when required for

image acquisition, photographer certification [8]. The CRCs are masked to study assignments and provide standardized grading of images from study subjects. There are instances where CRCs have been in the forefront of validating diagnostic equipment, and working alongside with academic and industry partners, they have developed relevant scales and imaging equipment that are commonly used in clinical trials [19,20]. CRCs adhere strictly to Good Clinical Practice (GCP) guidelines and have continuous quality control of images taken at sites. In addition, CRCs retrain technicians and investigators as necessary to ensure high quality standards since the image readouts are frequently used as primary or secondary endpoints. The Food and Drug Administration has a Guidance document that encourages sponsors to employ centralized image interpretation when developing a clinical trial protocol especially when using an image-based primary endpoint [21]. The role of CRCs have a critical role in the reliability of data, for example, the automated readouts from Optical Coherence Tomography (OCT) of the central retinal thickness is heavily dependent on correct segmentation by the OCT diagnostic unit. Segmentation errors are common and can cause clinically meaningful deviation in central retinal thickness measurements that can be averted with the use of a CRC [22,23].

A potential limitation in this study was the imbalance in the distribution of the Black/African American and Hispanic/Latino across the cohorts. Black/African American have been reported to have a higher incidence of MGD compared with Caucasians [24] so this uneven distribution between the non-MGD and MGD cohorts is not surprising. In addition, this clinical study employed investigators with a DED specialty and experience with meibum expression and grading. With large scale clinical trials in drug development for asset registration, it is not unusual to have dozens of sites with investigators that may not have this degree of experience to perform meibum quality grading. Adequate hands-on training for the inexperienced investigators is necessary to assure quality meibum grading at sites. This also speaks to the importance of developing the capabilities to perform quality imaging of the meibum secretion at the investigative sites with the use of a CRC, especially when conducting large multicenter registration studies where high-quality image acquisition is required. Artificial Intelligence (AI) based on Deep Learning have been applied to various ophthalmic images, with robust classification performance in detecting conditions like diabetic retinopathy and in the classification and grading of cataracts [25,26]. AI-assisted assessment of meibum secretion quality may also be in the future and can improve the accuracy in grading meibum quality secretions from video images.

In summary, MGD is commonly associated with DED and numerous clinical trials are being conducted to potentially approve therapies to treat this condition. CRCs are crucial entities in the conduct of clinical trials, ensuring the objectivity and integrity of study data, and helping to maintain the highest standards of GCP. In this pilot study, there was substantial level of agreement between investigator and CRC-assessed MMQS scores in cohorts with MGD, however, there was only fair agreement in participants without MGD. This may be due to meibum secretions that are often optically clear in subjects without MGD impacting the accuracy of the meibum score grading from a video image. Investigative sites using higher-resolution video imaging may lead to more accurate assessments at the CRC for future clinical studies in participants with MGD.

Table 1: A Composite Grading Scale for MGD Severity.

Cohort	Investigator-graded MMQS[a,b,c]	Schirmer Tear Test Without Anesthesia[b]	Sum of Scores of Worst 2 Symptoms on the Ocular Symptom Questionnaire
Non-MGD	0 or 1	≥7 mm/5 min	0 to 4 with neither symptom scored as >2
Mild/moderate MGD	2	≥7 mm/5 min	0 to 4 with neither symptom scored as >2
Severe MGD	3	≥7 mm/5 min	≥4

The cohort selection criteria specified by the latest study protocol amendment are listed.

[a]Six central glands in the lower lids of each eye were examined and the meibum quality of each gland was graded on a scale of 0 = clear excreta or clear with small particles (normal viscosity); 1 = opaque excreta with normal viscosity; 2 = opaque excreta with increased viscosity (gel-like); 3 = secretions retain shape, or secretions do not completely express but a toothpaste-like substance can be seen at the opening of the orifice; and NE = non expressible (nothing at orifice).

[b]MMQS and Schirmer test criteria must be met in the same eye (the study eye).

[c]None of the 6 central glands graded in the eye could have a meibum quality score greater than the maximum specified. MGD, meibomian gland dysfunction; MMQS, maximum meibum quality score among the 6 central glands in the lower lid that were graded.

MGD, meibomian gland dysfunction; MMQS, maximum meibum quality score among the 6 central glands in the lower lid that were graded.

Table 2: Subject Demographic Characteristics (Enrolled Population).

Characteristic	Non-MGD (n = 25)	Mild/Moderate MGD (n = 25)	Severe MGD (n = 25)	Total (n = 75)
Age, mean (SD), y	52.0 (8.34)	52.8 (6.26)	58.8 (11.86)	54.5 (9.49)
Range	40–74	43–63	41–89	40–89
<45, n (%)	4 (16)	4 (16)	3 (12)	11 (14.7)
45–65, n (%)	19 (76)	21 (84)	17 (68)	57 (76)
>65, n (%)	2 (8)	0	5 (20)	7 (9.3)

Characteristic	Non-MGD (n = 25)	Mild/Moderate MGD (n = 25)	Severe MGD (n = 25)	Total (n = 75)
Sex, n (%)				
Male	9 (36)	9 (36)	7 (28)	25 (33.3)
Female	16 (64)	16 (64)	18 (72)	50 (66.7)
Race, n (%)				
White	13 (52)	6 (24)	4 (16)	23 (30.7)
Black	7 (28)	15 (60)	11 (44)	33 (44)
Asian	1 (4)	1 (4)	2 (8)	4 (5.3)
Hispanic	1 (4)	2 (8)	8 (32)	11 (14.7)
Other	3 (12)	1 (4)	0	4 (5.3)

MGD: Meibomian Gland Dysfunction.

Table 3: MMQS Assessments of the Study Eye by the Investigator and the CRC.

	Enrollment/Day 1		
MMQS	Non-MGD (N = 25)	Mild/ Moderate MGD (N = 25)	Severe MGD (N = 25)
MMQS - Investigator Assessment			
N	25	25	25
0	17 (68.0%)	0	0
1	8 (32.0%)	0	0
2	0	25 (100%)	0
3	0	0	25 (100%)
p-values [a]	|-- < 0.001 --|		
		|-- < 0.001 --|	
	|-------- < 0.001 --------|		
mean (SD)	0.3 (0.48)	2.0 (0.00)	3.0 (0.00)
MMQS - CRC Assessment			
N	19	22	24
0	3 (15.8%)	1 (4.5%)	0
1	7 (36.8%)	4 (18.2%)	4 (16.7%)
2	4 (21.1%)	6 (27.3%)	2 (8.3%)
3	5 (26.3%)	11 (50.0%)	18 (75.0%)
p-values [a]	|--- 0.011 ---|		
		|-- 0.007 --|	
	|-------- 0.028 -------|		
mean (SD)	1.6 (1.07)	2.2 (0.92)	2.6 (0.78)

Note: MMQS scale: 0 = clear excreta or clear with small particles, normal viscosity. 1 = opaque excreta with normal viscosity. 2 = opaque excreta with increased viscosity, gel-like. 3 = secretions retain shape after expression or secretions do not express but a toothpaste-like substance can be seen at the opening of the orifice.

[a]Pairwise comparisons of cohorts, based on CMH method with modified ridit scores, stratified by site. Vertical bars (|), aligned with the column headings, indicate the cohorts compared.

Abbreviations: CMH: Cochran-Mantel-Haenszel; MGD: meibomian gland dysfunction; MMQS: maximum meibum quality score

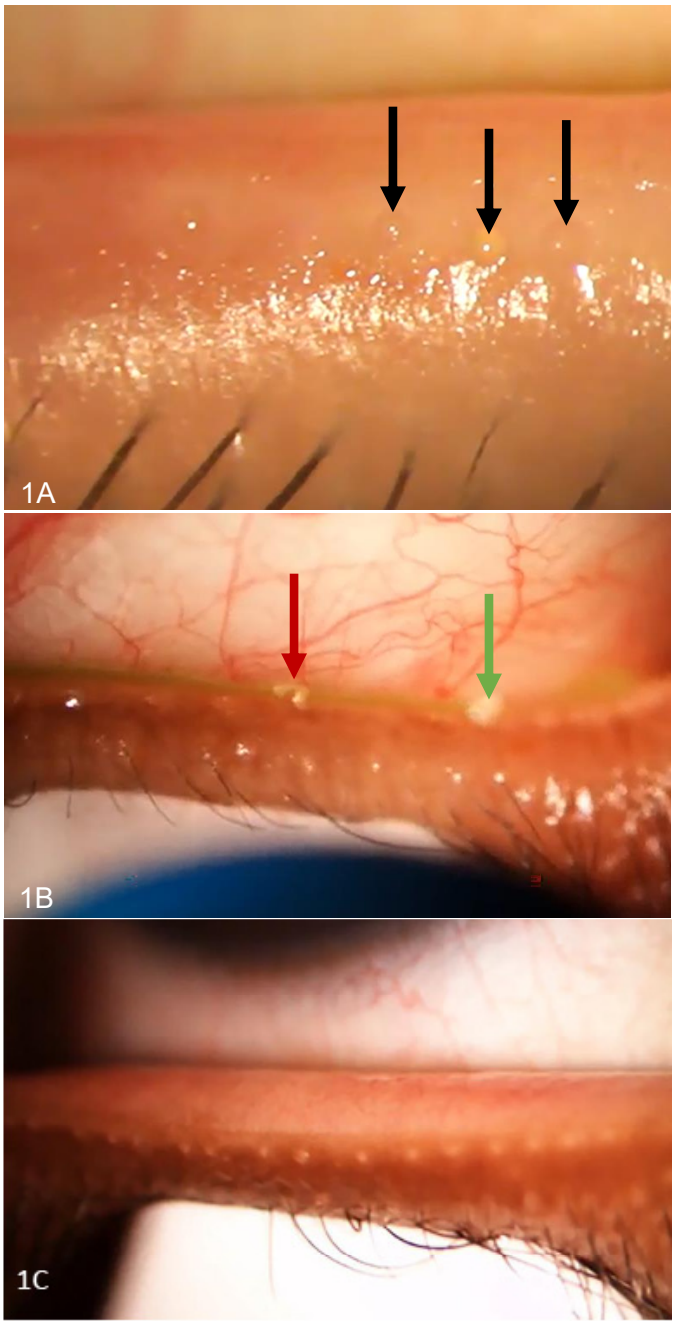
Figure 1: Lid Margin Images with pressure from the Meibomian Gland Evaluator™

(A) Grade 0 normal meibum secretions (black arrows).

(B) Grade 2 (green arrow) and 3 (red arrow) abnormal meibum secretions.

(C) Participant with meibomian gland ostia prolapse, mimicking pasty meibum secretions.

Figure C: Participant with meibomian gland ostia prolapse, mimicking pasty meibum secretions.



Data Sharing: AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execu-

tion of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Disclosures

K.K.N. Consultancy: Abbvie, Alcon, Aldeyra, Azura, Bausch + Lomb, Bruder, Cavalry, Dompe, HanAll Bio, Harrow, Novartis, Novaliq, Oyster Point Pharma/Viatris, Sydnexis, Tarsus, TearSolutions, Thea, Topcon, and Trukera.

Research fees from Aramis, Kowa, Science Based Health, Sylentis, and TearScience.

AN, CZ, XX, and MRR are full-time employees of AbbVie and may hold AbbVie stock. ITR and NA are interns at AbbVie. Allergan (prior to acquisition by AbbVie) funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Editorial support was provided by Angela T. Hadsell.

References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017; 15(3): 276-283. doi:10.1016/j.jtos.2017.05.008.
2. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011; 52(4): 1930-1937. doi:10.1167/iovs.10-6997b.
3. McCann P, Abraham AG, Mukhopadhyay A, et al. Prevalence and Incidence of Dry Eye and Meibomian Gland Dysfunction in the United States: A Systematic Review and Meta-analysis. JAMA Ophthalmol. 2022; 140(12): 1181-1192. doi:10.1001/jamaophthalmol.2022.4394.
4. Lemp MA, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: A retrospective study. 2012; 31(5): 472-478. doi:10.1097/ICO.0b013e318225415a.
5. White DE, Zhao Y, Ogundele A, et al. Real-World Treatment Patterns Of Cyclosporine Ophthalmic Emulsion And Lifitegrast Ophthalmic Solution Among Patients With Dry Eye. Clin Ophthalmol. 2019; 13(2285-2292). doi:10.2147/opth.S226168.
6. Zhao Y, Veerappan A, Yeo S, et al. Clinical Trial of Thermal Pulsation (LipiFlow) in Meibomian Gland Dysfunction With Preteatment Meibography. Eye Contact Lens. 2016; 42(6): 339-346. doi:10.1097/icl.0000000000000228.
7. Steven P, Augustin AJ, Geerling G, et al. Semifluorinated Alkane Eye Drops for Treatment of Dry Eye Disease Due to Meibomian Gland Disease. J Ocul Pharmacol Ther. 2017; 33(9): 678-685. doi:10.1089/jop.2017.0042.
8. Tan CS, Sadda SR. The role of central reading centers--current practices and future directions. Indian J Ophthalmol. 2015; 63(5): 404-405. doi:10.4103/0301-4738.159866.
9. Ajouz L, Nguyen A, Zhao C, et al. Exploring Signs and Symptoms Associated with Meibomian Gland Dysfunction for Use as Clinical Trial Endpoints. J Ocul Pharmacol Ther. 2023; 39(9): 611-621. doi:10.1089/jop.2023.0064.
10. Ajouz L, Hallak J, Naik R, et al. Evaluation of the Impact of Meibomian Gland Dysfunction Using a Novel Patient-Reported Outcome Instrument. J Ocul Pharmacol Ther. 2024; 40(1): 48-56. doi:10.1089/jop.2023.0080.
11. Nagar S, Ajouz L, Nichols KK, et al. Relationship Between Human Meibum Lipid Composition and the Severity of Meibomian Gland Dysfunction: A Spectroscopic Analysis. Invest Ophthalmol Vis Sci. 2023; 64(10): 22. doi:10.1167/iovs.64.10.22.
12. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: Report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011; 52(4): 2050-2064. doi:10.1167/iovs.10-6997g.
13. Tomlinson A, Bron AJ, Korb DR, et al. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci. 2011; 52(4): 2006-2049. doi:10.1167/iovs.10-6997f.
14. Mathers WD, Shields WJ, Sachdev MS, et al. Meibomian gland dysfunction in chronic blepharitis. 1991; 10(4): 277-285. doi:10.1097/00003226-199107000-00001.
15. Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. Br J Math Stat Psychol. 2008; 61(1): 29-48. doi:10.1348/000711006x126600.
16. Schmidl D, Bata AM, Szegedi S, et al. Influence of Perfluorohexyloctane Eye Drops on Tear Film Thickness in Patients with Mild to Moderate Dry Eye Disease: A Randomized Controlled Clinical Trial. J Ocul Pharmacol Ther. 2020; 36(3): 154-161. doi:10.1089/jop.2019.0092.
17. Tian L, Gao Z, Zhu L, et al. Perfluorohexyloctane Eye Drops for Dry Eye Disease Associated With Meibomian Gland Dysfunction in Chinese Patients: A Randomized Clinical Trial. JAMA Ophthalmol. 2023; 141(4): 385-392. doi:10.1001/jamaophthalmol.2023.0270.
18. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. 2008; 27(10): 1142-1147. doi:10.1097/ICO.0b013e3181814cff.
19. Benetz BA, Diaconu E, Bowlin SJ, et al. Comparison of corneal endothelial image analysis by Konan SP8000 noncontact and Bio-Optics Bambi systems. 1999; 18(1): 67-72.
20. McCarey BE, Edelhauser HF, Lynn MJ. Review of corneal endothelial specular microscopy for FDA clinical trials of refractive procedures, surgical devices, and new intraocular drugs and solutions. 2008; 27(1): 1-16. doi:10.1097/ICO.0b013e31815892da.
21. US Food, Drug Administration. Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. 2018. https://digirepo.nlm.nih.gov/master/borndig/101734178/UCM268555.pdf.
22. Decroos FC, Stinnett SS, Heydary CS, et al. Reading Center Characterization of Central Retinal Vein Occlusion Using Optical Coherence Tomography During the COPERNICUS Trial. Transl Vis Sci Technol. 2013; 2(7): 7. doi:10.1167/tvst.2.7.7.
23. Glassman AR, Beck RW, Browning DJ, et al. Comparison of optical coherence tomography in diabetic macular edema, with and without reading center manual grading from a clinical trials perspective. Invest Ophthalmol Vis Sci. 2009; 50(2): 560-566. doi:10.1167/iovs.08-1881.
24. Eballé AO, Ellong A, Wang RE, et al. Meibomian glands dysfunction and ocular surface in black people. J Fr Ophtalmol. 2019; 42(2): 127-132. doi:10.1016/j.jfo.2018.06.008.

25. Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol. 2019; 103(2): 167-175. doi:10.1136/bjophthalmol-2018-313173.

26. Son H, Lee S, Kim K, et al. Deep learning-based quantitative estimation of lymphedema-induced fibrosis using three-dimensional computed tomography images. 2022; 12(1): 15371. doi:10.1038/s41598-022-19204-6.