Assessment of Retinal Morphology with Spectral and Time Domain OCT in the Phase III Trials of Enzymatic Vitreolysis

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PURPOSE. To determine the relative ability of time domain (TD)-optical coherence tomography (OCT) compared with spectral domain (SD)-OCT to assess vitreoretinal interface abnormalities and pharmacologic treatment of symptomatic vitreomacular adhesion (VMA)/traction (VMT) with or without full-thickness macular hole (FTMH), and the reproducibility of trained readers' evaluation of these images in an interventional phase III program of ocriplasmin.

METHODS. Eyes from the MIVI-TRUST program with concurrent SD-OCT and TD-OCT at baseline and day 28 were included. Pairwise intermodality agreement frequency and interreader reproducibility were calculated for baseline OCT features and the study endpoints of VMA resolution and FTMH closure.

RESULTS. A total 186 eyes (186 patients) met the inclusion criteria for this study. There was excellent agreement between TD-OCT and SD-OCT for the reader-determined presence or absence of VMA (96.7%), FTMH (97.1%), and all other baseline parameters except epiretinal membrane (84.3%), which was detected at a significantly greater rate with SD-OCT than TD-OCT (44.6% vs. 35.5%, P < 0.001). There was excellent agreement for the study endpoints of VMA resolution (95.4%) and FTMH closure (100%) at day 28. Interreader reproducibility was similar but consistently greater with SD-OCT than TD-OCT to detect baseline VMA (kappa 0.6 vs. 0.52); FTMH (kappa 0.9 vs. 0.78); and epiretinal membrane (kappa 0.65 vs. 0.45).

CONCLUSIONS. Readers using SD-OCT or TD-OCT have similar ability to assess vitreoretinal interface abnormalities and outcomes of enzymatic vitreolysis. SD-OCT may be superior for formal clinical trial grading due to greater interreader reproducibility and, therefore, decreased need for arbitration of discrepant values. (ClinicalTrials.gov numbers, NCT00781859, NCT00798317.) (Invest Ophthalmol Vis Sci. 2012;53:7395–7401) DOI:10.1167/iovs.12-10379
efficacy of a single 125-mg ocirplasmin intravitreal injection (Thrombo-
Genics NV, Leuven, Belgium) with a single placebo injection for
obtaining VMA release without vitrectomy. The MIVI-TRUST program
recruited 652 subjects from 90 centers across the United States and
Europe. One eye with symptomatic VMA/MT was enrolled per
subject, according to inclusion and exclusion criteria that have been
previously described. All subjects received thorough counseling,
signed a written informed consent form prior to enrollment in the
program, and then were followed for 6 months with serial OCT scans
obtained at each visit. The trial procedures were approved by the
institutional review board (IRB) at each participating study site. The
present study was approved by the Duke University IRB and followed
the tenets of the Declaration of Helsinki.

In the present study, we enrolled all eyes in the MIVI-TRUST
program that had paired TD-OCT and SD-OCT images for the baseline
visit and for the day 28 clinical endpoint visit. Eyes were excluded if
they were missing either TD-OCT or SD-OCT scans at either visit. In the
MIVI-TRUST program, all study centers were required to use the same
OCT equipment (Stratus OCT, software version 6.0; Carl Zeiss Meditec,
Dublin, CA) for TD-OCT imaging at each study visit. Technicians were
certified for these trials and followed a scan protocol emphasizing
appropriate focus, saturation, and scan line placement.

The Stratus OCT protocol for each visit required a macular
thickness map (MTM) and a fast macular thickness (FTM) map, each
consisting of six equally spaced, 6-mm radial lines centered on the
fovea and separated 30° apart in a rotational manner. Each radial line
was comprised of 512 A-scans per line for MTM and 128 A-scans per
line for FTM, with an axial resolution of 10 μm per pixel. The protocol
also required a 10-mm vertical crosshair scan at 90° through the optic
disc, a 10-mm horizontal crosshair scan at 180° through the optic disc,
and a 10-mm offset high-resolution scan through the center of the fovea
and the optic disc. This offset scan line was angled at 5° for right eyes
and 355° for left eyes.

Two SD-OCT devices with distinct imaging protocols, the Cirrus
HD-OCT (software version 5.2; Carl Zeiss Meditec, Dublin, CA) and
Spectralis OCT (software version 5.3; Heidelberg Engineering,
Carlsbad, CA), were used in the SD-OCT substudy. For Cirrus, three
volumetric scan patterns with an axial resolution of 5 μm per pixel
were obtained. These patterns included a macular volume cube that
covered a 6-mm × 6-mm area of the retina with 128 horizontal line
scans and 512 A-scans per line, an optic nerve cube that covered a 6-
mm × 6-mm area of the retina with 200 horizontal line scans and 200 A-
scans per line, and a line raster scan that consisted of five consecutive
6-mm horizontal high-resolution scan lines spaced 250 μm apart
(covering a 6-mm × 1-mm area centered on the fovea) with 4096 A-
scans per line. For Spectralis, two volumetric 30° × 15° raster scan
patterns were obtained, covering an 8.6-mm × 4.3-mm area of the
retina. Each volumetric pattern was composed of 19 consecutive
horizontal high-resolution scan lines, spaced 240 μm apart, with 1536
A-scans per line and an axial resolution of 4 μm per pixel. One volume
pattern was centered on the fovea. The second volume pattern was
centered between the fovea and the optic disc, covering both regions.

All OCT scans from the MIVI-TRUST phase III program were
submitted to the Duke Reading Center (Duke University, Durham, NC),
where the coded scans for a given subject and visit date were graded by
two certified readers in a masked and independent manner. A data
specialist entered all concordant values from the two readers into the
trial database and flagged all discrepant values. A third certified senior
reader arbitrated the discrepant values. The senior reader reconciled all
reader disagreements according to his best judgment and expertise,
recording his decision as the final arbitrated value that the data
specialist entered into the trial database. All reader disagreements that
remained controversial despite arbitration were presented to the
director of grading (CAT) or the reading center director (Gig) for a final
decision. Each OCT variable was graded as present, absent, or unreadable (due to poor quality or centration of the scan), according
to either the agreed decision between masked readers or the arbitrated
decision when the readers disagreed. After finishing arbitration and
data entry, another masked data specialist or project manager verified
the accuracy of all values entered into the trial database. The verified
data were used to compare TD- and SD-OCT agreement on each study
variable.

VMA was defined on OCT as attachment of the posterior vitreous
hyaloid to the macula with vitreous detachment visible on opposite
sides of the adhesion site. Based on examination of one or more OCT B-
scans within the central 6-mm field. VMA width was graded
categorically based on whether the widest site of adhesion to the
macula was broad (>1500 μm), focal (<1500 μm), or could not be
determined. For multifocal VMA sites with intervening vitreous
detachment, the VMA width was determined by the greatest sum of
attachment widths in a single radial or raster line scan. Subparameters
of VMA included adhesions associated with FTMH, ERM, or central
foveal deformation. Additional graded categorical variables included
the following: FTMH, lamellar hole or pseudohole (LH/PH), macular
hole operculum, ERM, inner retinal or foveal deformation by ERM,
intraretinal cystoid spaces representing CME, subretinal fluid (SRF),
and retinoschisis (RS) defined as retinal splitting beyond the central 1-
mm diameter of the fovea. Additional subparameters included CME or
SRF within 500 μm from the foveal center.

Categorical data were reported as the percent frequency of
occurrence based on final arbitrated values. If an OCT variable was
graded as unreadable for any subject, then the subject’s data point
was excluded from analysis of the total paired agreement for this
variable. The agreement of TD-OCT versus SD-OCT for each of these
features was reported as the percent agreement and the Cohen
kappa coefficient with 95% confidence intervals (CI). Pairwise
comparisons of statistical significance and symmetry of agreement
for each parameter were performed with the McNemar-Bowker χ²
test, where P < 0.05 was considered statistically significant. The
same tests were repeated to determine the paired agreement of
Stratus TD-OCT with each specific SD-OCT device, Cirrus and
Spectralis.

Interreader reproducibility for TD-OCT and SD-OCT grading was
defined as the initial agreement between two certified readers to detect
VMA and associated OCT features prior to arbitration. Reader
agreement for a variable detected with one OCT modality was
determined by the difference of the total number of eligible eyes
graded and the number of eyes requiring arbitration due to discordant
values. Interreader reproducibility for TD-OCT and SD-OCT was
compared by reporting the percent reader agreement and the Cohen
kappa coefficient with 95% CI for each parameter. Statistical analyses
were performed with statistical modeling software (SAS JMP Pro 9.0;
SAS Institute, Inc., Cary, NC).

Results
Paired Comparison of SD-OCT versus TD-OCT
A total of 186 eyes (186 subjects) from 30 centers participating in
the MIVI-TRUST program met the enrollment criteria for this
study. Among this cohort, there were 86 right eyes and 100 left
eyes. A total of 744 OCT scans were evaluated, consisting of
SD-OCT and TD-OCT for baseline and day 28 visits for all 186
enrolled eyes.

Readers detected baseline VMA-associated pathology with
similar frequency on SD-OCT and TD-OCT for nearly all
parameters. Only the frequency of ERM detection differed
significantly (SD-OCT 45% versus TD-OCT 35%). Among eyes
with agreement on baseline VMA or baseline FTMH from
paired SD-OCT and TD-OCT scans, the primary trial endpoint
of VMA resolution and the secondary trial endpoint of FTMH
closure at day 28 were detected with equal frequency by both
machines (Table 1).

Concordance, defined as the percent agreement between
OCT modalities when the pathology was present or absent,
was excellent for baseline VMA (97%) and VMA-associated pathology. Concordance for the presence or absence of ERM (84%) was the lowest among all baseline parameters. There was excellent concordance (95%) for VMA resolution and perfect concordance (100%) for FTMH closure at day 28 (Table 2).

A post hoc review of spectral and time domain OCT imaging was performed in eyes with OCT modality disagreement for baseline VMA, FTMH, or day 28 VMA resolution. With SD-OCT raster scans, readers failed to detect baseline VMA in four eyes, baseline FTMH in four eyes, and persistent day 28 VMA in three eyes that were detected with TD-OCT radial scans (Fig. 1). However, with TD-OCT radial scans centered on the fovea, readers failed to detect baseline FTMH in one eye and persistent day 28 VMA in two eyes that had eccentric pathology detected with SD-OCT raster scans. With TD-OCT, readers also failed to detect baseline VMA in two eyes and day 28 VMA in three eyes that were detected with SD-OCT due to greater signal strength at the vitreoretinal interface and posterior vitreous cortex (Fig. 2).

### Paired Comparison of Specific SD-OCT Machines versus TD-OCT

In this study, SD-OCT scans were obtained with Cirrus from 119 eyes and with Spectralis from 67 eyes. Readers detected baseline VMA and FTMH with similar frequency when comparing Cirrus with Stratus and when comparing Spectralis with Stratus. ERM was detected significantly more frequently with Cirrus than with Stratus (Fig. 3). Similarly, ERM was detected more frequently with Spectralis than with Stratus, but this difference did not reach statistical significance. Each SD-OCT machine, when compared with Stratus, identified with similar frequency the study endpoints of VMA resolution and FTMH closure (Table 3).

Concordance of each specific SD-OCT machine with Stratus was excellent for baseline VMA and FTMH, but concordance was lower for ERM. Concordance for VMA resolution was excellent for Cirrus (95%) and Spectralis (97%) with respect to Stratus. Concordance for FTMH closure was perfect (100%) for both Cirrus and Spectralis with respect to Stratus (Table 4).

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**Table 1.** Frequency of Pathology and Study Endpoints Detected with SD- versus TD-OCT among Eyes with Dual Imaging

<table>
<thead>
<tr>
<th>Group</th>
<th>SD-OCT</th>
<th>TD-OCT</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline foveal VMA</td>
<td>93.6% (174/186)</td>
<td>94.6% (176/186)</td>
<td>0.89</td>
</tr>
<tr>
<td>Broad (&gt;1500 μm)</td>
<td>21.7% (36/166)</td>
<td>22.3% (37/166)</td>
<td>0.76</td>
</tr>
<tr>
<td>Focal (≤1500 μm)</td>
<td>79.5% (130/166)</td>
<td>77.7% (129/166)</td>
<td>0.52</td>
</tr>
<tr>
<td>Deformation by VMA</td>
<td>90.1% (164/182)</td>
<td>92.3% (168/182)</td>
<td>0.32</td>
</tr>
<tr>
<td>Resolution of VMA</td>
<td>20.6% (36/175)</td>
<td>21.7% (38/175)</td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline FTMH</td>
<td>20.8% (36/175)</td>
<td>22.5% (39/173)</td>
<td>0.18</td>
</tr>
<tr>
<td>Closure of FTMH</td>
<td>40.0% (14/35)</td>
<td>40.0% (14/35)</td>
<td>1.0</td>
</tr>
<tr>
<td>Baseline LH/PH</td>
<td>11.1% (19/171)</td>
<td>10.5% (18/171)</td>
<td>0.81</td>
</tr>
<tr>
<td>Baseline ERM</td>
<td>44.6% (82/184)</td>
<td>35.3% (65/184)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline Retinoschisis</td>
<td>13.3% (23/173)</td>
<td>11.6% (20/173)</td>
<td>0.55</td>
</tr>
<tr>
<td>Baseline CME</td>
<td>83.9% (151/180)</td>
<td>81.7% (147/180)</td>
<td>0.32</td>
</tr>
<tr>
<td>Central 1-mm CME</td>
<td>99.3% (140/141)</td>
<td>96.5% (136/141)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline SRF</td>
<td>42.0% (75/174)</td>
<td>42.0% (75/174)</td>
<td>1.0</td>
</tr>
<tr>
<td>Central 1-mm SRF</td>
<td>98.4% (60/61)</td>
<td>98.4% (60/61)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*McNemar-Bowker χ² test for disagreement.

**Table 2.** Concordance of Pathology and Study Endpoints Detected with SD- versus TD-OCT among Eyes with Dual Imaging

<table>
<thead>
<tr>
<th>Group</th>
<th>SD and TD Agree Yes</th>
<th>SD and TD Agree No</th>
<th>SD Yes TD No</th>
<th>TD Yes SD No</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline foveal VMA</td>
<td>92.4% (172/186)</td>
<td>4.5% (8/186)</td>
<td>1.1% (2/186)</td>
<td>2.2% (4/186)</td>
<td>0.57 (0.36–0.79)</td>
</tr>
<tr>
<td>Broad (&gt;1500 μm)</td>
<td>18.7% (31/166)</td>
<td>74.7% (124/166)</td>
<td>3.0% (5/166)</td>
<td>3.6% (6/166)</td>
<td>0.81 (0.70–0.92)</td>
</tr>
<tr>
<td>Focal (≤1500 μm)</td>
<td>74.7% (124/166)</td>
<td>18.7% (31/166)</td>
<td>3.6% (6/166)</td>
<td>3.6% (6/166)</td>
<td>0.81 (0.70–0.92)</td>
</tr>
<tr>
<td>Deformation by VMA</td>
<td>86.8% (158/182)</td>
<td>4.4% (8/182)</td>
<td>3.3% (6/182)</td>
<td>5.5% (10/182)</td>
<td>0.45 (0.23–0.68)</td>
</tr>
<tr>
<td>Resolution of VMA</td>
<td>18.9% (35/175)</td>
<td>76.5% (134/175)</td>
<td>1.7% (3/175)</td>
<td>2.9% (5/175)</td>
<td>0.86 (0.77–0.96)</td>
</tr>
<tr>
<td>Baseline FTMH</td>
<td>20.2% (35/173)</td>
<td>76.9% (133/173)</td>
<td>0.6% (1/173)</td>
<td>2.3% (4/173)</td>
<td>0.91 (0.84–0.99)</td>
</tr>
<tr>
<td>Closure of FTMH</td>
<td>40.0% (14/35)</td>
<td>60.0% (21/35)</td>
<td>0</td>
<td>0</td>
<td>0.01 (0.00–0.99)</td>
</tr>
<tr>
<td>Baseline LH/PH</td>
<td>5.8% (10/171)</td>
<td>84.2% (144/171)</td>
<td>5.3% (9/171)</td>
<td>4.7% (8/171)</td>
<td>0.48 (0.27–0.70)</td>
</tr>
<tr>
<td>Baseline ERM</td>
<td>32.1% (59/184)</td>
<td>52.2% (96/184)</td>
<td>12.5% (23/184)</td>
<td>3.2% (6/184)</td>
<td>0.67 (0.57–0.78)</td>
</tr>
<tr>
<td>Baseline Retinoschisis</td>
<td>5.2% (9/175)</td>
<td>80.3% (139/175)</td>
<td>8.1% (14/173)</td>
<td>6.4% (11/173)</td>
<td>0.33 (0.13–0.54)</td>
</tr>
<tr>
<td>Baseline CME</td>
<td>78.3% (141/180)</td>
<td>12.8% (23/180)</td>
<td>5.6% (10/180)</td>
<td>3.3% (6/180)</td>
<td>0.69 (0.55–0.85)</td>
</tr>
<tr>
<td>Central 1-mm CME</td>
<td>95.7% (135/141)</td>
<td>0</td>
<td>3.6% (5/141)</td>
<td>0.7% (1/141)</td>
<td>0.72 (0.55–0.85)</td>
</tr>
<tr>
<td>Baseline SRF</td>
<td>35.1% (61/174)</td>
<td>51.1% (89/174)</td>
<td>6.9% (12/174)</td>
<td>6.9% (12/174)</td>
<td>0.72 (0.61–0.82)</td>
</tr>
<tr>
<td>Central 1-mm SRF</td>
<td>98.4% (60/61)</td>
<td>1.6% (1/61)</td>
<td>0</td>
<td>0</td>
<td>0.01 (0.00–0.99)</td>
</tr>
</tbody>
</table>

FTMH <400 μm.
Interreader Reproducibility of SD-OCT versus TD-OCT Grading

Tables 5 and 6 present interreader reproducibility at baseline and day 28, respectively. For baseline visits, all 186 study eyes had initial reader values available for reproducibility analysis. For day 28 visits, 185 study eyes had initial reader values available. At baseline, SD-OCT had higher interreader agreement, and therefore lower rate of arbitration than TD-OCT for all parameters (Table 5). At day 28, SD-OCT had higher interreader reproducibility than TD-OCT for all parameters except OCT features associated with ERM (Table 6). At baseline and day 28, with both OCT modalities, interreader reproducibility was greatest for FTMH. At baseline, with both OCT modalities, interreader reproducibility was lowest for broad versus focal VMA. At day 28, reproducibility with TD-OCT was lowest for broad versus focal VMA, but reproducibility with SD-OCT was lowest for ERM with central foveal deformation.

**DISCUSSION**

In this report, we found that certified readers detected baseline VMA, OCT features associated with VMA, and the trial endpoints of VMA resolution and FTMH closure, with very similar rates on SD-OCT and TD-OCT imaging. We also observed similar rates in a comparison of pathology grading between TD-OCT and two specific widely used SD-OCT instruments. The interreader grading reproducibility was generally high for both OCT modalities, although the agreement among primary readers for baseline pathology was greater on SD-OCT than TD-OCT. We included only a subset of eyes from the MIVI-TRUST phase III program that had dual OCT imaging; therefore, this study was not designed to verify the previously reported efficacy of ocriplasmin on the treatment of symptomatic VMA/VMT and macular hole.10

Studies to determine agreement of TD-OCT and SD-OCT quantitative and qualitative parameters have been reported previously for neovascular AMD,13–15 diabetic macular edema,13,16 and uveitis.13,17 These reports suggest that OCT machines should not be used interchangeably for quantitative retinal thickness measurements of healthy and pathologic eyes.13,18–20 To the best of our knowledge, literature is absent that evaluates the relative merits of TD-OCT and SD-OCT for evaluating vitreoretinal interface disorders in prospective clinical trials. With the transition from TD-OCT to SD-OCT imaging in randomized clinical trial protocols, there is now a greater need to understand the impact that spectral domain technology would have had on trial outcomes determined by TD-OCT.

This study analyzed prospective data from the MIVI-TRUST program, and showed that readers can effectively assess baseline VMA and associated pathology with both time domain and spectral domain OCT. Discrepancies in the assessment of VMA
most often were the result of differences in the area sampled by the radial versus raster line orientation of the scanning protocols, and not due to advantages in spatial resolution. This finding suggests that a combination of radial and parallel line scans with either OCT modality will improve the accuracy of OCT grading more than a single-orientation volumetric scan obtained with time domain or spectral domain OCT.

The only anatomic feature that was detected at a significantly different rate by SD-OCT than with TD-OCT was ERM, although the detection discrepancy was still much lower than that reported previously. In a study of eyes with a clinical diagnosis of ERM, Falkner-Radler et al. found that well-differentiated ERM was detected in 61% by SD-OCT grading, but only 32% by TD-OCT. In the present study, ERM was detected by SD-OCT but not TD-OCT in approximately 12% of evaluated eyes. We speculate that SD-OCT readers detected ERM more often than TD-OCT readers for two reasons. First, higher axial resolution leads to superior visualization of separations between ERM and the internal limiting membrane. Second, greater scanning density with the SD-OCT raster protocol permits observation of small sites of ERM separation. These results imply that TD-OCT trial results for ERM should be interpreted with caution.

The relative ability of clinicians to use SD-OCT when compared with TD-OCT in daily clinical practice to detect VMA and associated pathology remains unclear. In the present report, certified OCT readers were trained to carefully review all radial scans obtained with Stratus, or all raster scans in volume cubes obtained with Cirrus and Spectralis. We hypothesize that if clinicians adopt this technique and review the entire available scan, both types of machines will enable nearly equal detection of VMA and most types of associated pathology, with the exception of ERM. We expect that clinicians will be able to identify ERM more frequently with SD-OCT, for reasons mentioned above.

Interreader grading reproducibility was generally high with both spectral and time domain OCT. We and others have reported high quantitative and qualitative inter- and intrareader reproducibility with TD-OCT in eyes with neovascular AMD, and with SD-OCT in healthy eyes. We have recently reported excellent intrareader reproducibility for TD-OCT grading of baseline VMA, broad versus focal VMA width, baseline FTMH, and baseline ERM in the MIVI-TRUST program. In the present study, we found a similar high degree of interreader reproducibility with both spectral and time domain OCT for most parameters assessed. Of the parameters measured, readers agreed least when differentiating broad from focal VMA, on both TD-OCT and SD-OCT images. To determine broad versus focal VMA, readers measured the macular adhesion maximum transverse width. The measurement variability among readers was likely due to two factors: first, higher subjectivity among readers in measuring horizontal VMA width, relative to scoring other VMA-associated pathology; and second, different sectioning

![Figure 3. OCT nonconcordance of epiretinal membrane (ERM) between TD-OCT and SD-OCT modalities. (A) ERM was not detected by TD-OCT readers at the site of inner retinal hyperreflectivity adjacent to VMA. (B) Visible separation of ERM from inner retinal surface (arrow) allowed SD-OCT readers to detect the ERM adjacent to VMA.](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Eyes (no. of eyes/total eyes)</th>
<th>SD-OCT</th>
<th>TD-OCT</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus (n = 119)</td>
<td>Baseline foveal VMA</td>
<td>94.1% (112/119)</td>
<td>95.0% (113/119)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Resolution of VMA</td>
<td>21.2% (24/112)</td>
<td>23.0% (26/112)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Baseline FTMH</td>
<td>26.6% (29/109)</td>
<td>26.6% (29/109)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Closure of FTMH</td>
<td>46.4% (13/28)</td>
<td>46.4% (13/28)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Baseline ERM</td>
<td>45.3% (53/117)</td>
<td>35.3% (39/117)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spectralis (n = 67)</td>
<td>Baseline foveal VMA</td>
<td>92.5% (62/67)</td>
<td>94.0% (63/67)</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Resolution of VMA</td>
<td>19.4% (12/62)</td>
<td>19.4% (12/62)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Baseline FTMH</td>
<td>10.9% (7/64)</td>
<td>15.6% (10/64)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Closure of FTMH</td>
<td>14.3% (1/7)</td>
<td>14.3% (1/7)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Baseline ERM</td>
<td>43.3% (29/67)</td>
<td>38.8% (26/67)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

FTMH <400 μm.

* McNemar-Bowker $\chi^2$ test for disagreement.
patterns—radial versus raster line orientation—for the two modalities. In previous reports, the maximum vitreomacular traction width has been highly variable, ranging from 3500 to 6000 μm in pilot studies of 7 to 19 eyes. Not only does VMA have highly variable horizontal diameters, but OCT reconstructions of VMA often reveal asymmetric conoid adhesions to retinal tissue that may create ambiguity among readers or clinicians when choosing the horizontal plane in which to take measurements. We could not find previous reproducibility studies of VMA width measurement, so we currently have no basis with which to compare this finding in the present study.

Although grading reproducibility was generally high, it was modestly but consistently higher among SD-OCT readers on all baseline parameters and most day 28 parameters. According to our reading center protocols, discrepant values produced by a masked reader pairs were submitted to a senior reader who arbitrated each disagreement. Since fewer discrepant values required arbitration with SD-OCT, less time dedicated to the arbitration process would result in greater efficiency of data collection during SD-OCT grading. However, this increased efficiency is offset somewhat by the increased time required for readers to review each SD-OCT scan volume, due to the greater number of scan lines that must be examined in a spectral domain macular volume cube than in a TD-OCT macular thickness map. Further grading time studies would be needed to assess the relative overall efficiency of spectral and time domain OCT grading efficiency in a reading center setting.

In conclusion, our results indicate that both TD-OCT and SD-OCT grading processes can be effectively used to assess the morphology of vitreoretinal interface disorders in multicenter clinical trials. Our results also show that trained readers can assess pharmacologic vitreolysis equally with TD-OCT and SD-OCT. The pairwise comparison of TD-OCT with SD-OCT validates the TD-OCT grading protocol for MIVI-TRUST and the data obtained from this clinical interventional program. However, for the purpose of formal OCT grading for multicenter clinical trials, SD-OCT may be slightly superior due to increased initial reader agreement and, therefore, increased efficiency in the grading process. New clinical trials will inevitably transition to SD-OCT imaging exclusively, but for the purpose of scientific discussion, the results reported in future trials based exclusively on SD-OCT can be confidently compared to the results obtained from this phase III program.

**Acknowledgments**

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**References**


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**Table 4.** Concordance and Distribution of Grading for Cirrus and Spectralis versus Stratus among Eyes with Dual Imaging

<table>
<thead>
<tr>
<th>Group</th>
<th>SD and TD Agree Yes</th>
<th>SD and TD Agree No</th>
<th>SD Yes TD No</th>
<th>TD Yes SD No</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus (n = 119)</td>
<td>93.3% (111/119)</td>
<td>4.3% (5/119)</td>
<td>0.8% (1/119)</td>
<td>1.6% (2/119)</td>
<td>0.60 (0.33–0.87)</td>
</tr>
<tr>
<td>Baseline foveal VMA</td>
<td>91.0% (61/67)</td>
<td>4.5% (3/67)</td>
<td>1.5% (1/67)</td>
<td>3.0% (2/67)</td>
<td>0.53 (0.18–0.88)</td>
</tr>
<tr>
<td>Resolution of VMA</td>
<td>17.8% (11/62)</td>
<td>79.0% (49/62)</td>
<td>1.6% (1/62)</td>
<td>1.6% (1/62)</td>
<td>0.90 (0.76–1.04)</td>
</tr>
<tr>
<td>Baseline FTMH</td>
<td>10.9% (7/64)</td>
<td>84.4% (54/64)</td>
<td>0</td>
<td>4.7% (3/64)</td>
<td>0.80 (0.58–1.02)</td>
</tr>
<tr>
<td>Closure of FTMH</td>
<td>14.3% (1/7)</td>
<td>85.7% (6/7)</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Baseline ERM</td>
<td>32.8% (22/67)</td>
<td>50.7% (34/67)</td>
<td>10.5% (7/67)</td>
<td>6.0% (4/67)</td>
<td>0.66 (0.48–0.84)</td>
</tr>
</tbody>
</table>

**Table 5.** Baseline Interreader Agreement with SD- versus TD-OCT

<table>
<thead>
<tr>
<th>Group</th>
<th>SD Reader Agreement</th>
<th>Kappa (95% CI)</th>
<th>TD Reader Agreement</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal VMA</td>
<td>80.1% (149/186)</td>
<td>0.60 (0.49–0.72)</td>
<td>75.8% (141/186)</td>
<td>0.52 (0.39–0.64)</td>
</tr>
<tr>
<td>Broad vs. focal VMA*</td>
<td>73.1% (136/186)</td>
<td>0.46 (0.34–0.59)</td>
<td>60.8% (113/186)</td>
<td>0.22 (0.07–0.36)</td>
</tr>
<tr>
<td>FTMH</td>
<td>95.2% (177/186)</td>
<td>0.90 (0.84–0.96)</td>
<td>88.2% (164/186)</td>
<td>0.78 (0.70–0.87)</td>
</tr>
<tr>
<td>ERM</td>
<td>82.3% (155/186)</td>
<td>0.90 (0.54–0.75)</td>
<td>72.6% (135/186)</td>
<td>0.45 (0.32–0.58)</td>
</tr>
<tr>
<td>Any retinal deformation by ERM</td>
<td>86.6% (161/186)</td>
<td>0.73 (0.63–0.83)</td>
<td>78.0% (145/186)</td>
<td>0.56 (0.44–0.68)</td>
</tr>
<tr>
<td>Central 1-mm retinal deformation by ERM</td>
<td>80.1% (149/186)</td>
<td>0.60 (0.49–0.72)</td>
<td>77.4% (144/186)</td>
<td>0.55 (0.43–0.67)</td>
</tr>
<tr>
<td>ERM at the site of VMA</td>
<td>81.7% (152/186)</td>
<td>0.63 (0.52–0.75)</td>
<td>78.0% (145/186)</td>
<td>0.56 (0.44–0.68)</td>
</tr>
<tr>
<td>CME</td>
<td>88.7% (165/186)</td>
<td>0.77 (0.68–0.87)</td>
<td>83.3% (155/186)</td>
<td>0.67 (0.56–0.77)</td>
</tr>
<tr>
<td>SRF</td>
<td>85.5% (159/186)</td>
<td>0.71 (0.61–0.81)</td>
<td>78.5% (146/186)</td>
<td>0.57 (0.45–0.69)</td>
</tr>
</tbody>
</table>

FTMH <400 μm.

* Modified Cohen Kappa for grading as VMA width broad, focal, or unable to determine.
### Table 6. Day 28 Interreader Agreement with SD- versus TD-OCT

<table>
<thead>
<tr>
<th>Group</th>
<th>SD Reader Agreement % Eyes (no. of eyes/total eyes)</th>
<th>Kappa (95% CI)</th>
<th>TD Reader Agreement % Eyes (no. of eyes/total eyes)</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal VMA</td>
<td>86.5% (160/185)</td>
<td>0.73 (0.63–0.83)</td>
<td>77.8% (144/185)</td>
<td>0.56 (0.44–0.68)</td>
</tr>
<tr>
<td>Broad vs. focal VMA*</td>
<td>77.8% (144/185)</td>
<td>0.56 (0.44–0.68)</td>
<td>73.5% (136/185)</td>
<td>0.47 (0.34–0.60)</td>
</tr>
<tr>
<td>FTMH</td>
<td>96.8% (179/185)</td>
<td>0.94 (0.88–0.99)</td>
<td>90.8% (168/185)</td>
<td>0.82 (0.73–0.90)</td>
</tr>
<tr>
<td>ERM</td>
<td>81.6% (151/185)</td>
<td>0.63 (0.52–0.74)</td>
<td>80.0% (148/185)</td>
<td>0.60 (0.48–0.72)</td>
</tr>
<tr>
<td>Central 1-mm retinal deformation by ERM</td>
<td>81.1% (150/185)</td>
<td>0.62 (0.51–0.73)</td>
<td>81.1% (150/185)</td>
<td>0.62 (0.51–0.73)</td>
</tr>
<tr>
<td>ERM at the site of VMA</td>
<td>76.8% (142/185)</td>
<td>0.54 (0.41–0.66)</td>
<td>78.9% (146/185)</td>
<td>0.58 (0.46–0.70)</td>
</tr>
<tr>
<td>CME</td>
<td>94.1% (174/185)</td>
<td>0.88 (0.81–0.95)</td>
<td>80.0% (148/185)</td>
<td>0.60 (0.48–0.72)</td>
</tr>
<tr>
<td>SRF</td>
<td>89.2% (165/185)</td>
<td>0.78 (0.69–0.87)</td>
<td>81.6% (151/185)</td>
<td>0.63 (0.52–0.74)</td>
</tr>
</tbody>
</table>

* Modified Cohen Kappa for grading VMA width as broad, focal, or unable to determine.

**Note:** SD = spectral-domain; TD = time-domain; FTMH = fine-tuned macular hole; VMA = vitreomacular adhesion; ERM = epiretinal membrane.

**References:**


