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Pneumatic Vitreolysis with Perfluoropropane for Vitreomacular Traction with and without Macular Hole

DRCR Retina Network Protocols AG and AH

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Purpose: To evaluate pneumatic vitreolysis (PVL) in eyes with vitreomacular traction (VMT) with and without full-thickness macular hole (FTMH).

Design: Two multicenter (28 sites) studies: a randomized clinical trial comparing PVL with observation (sham injection) for VMT without FTMH (Protocol AG) and a single-arm study assessing PVL for FTMH (Protocol AH).

Participants: Participants were adults with central VMT (vitreomacular adhesion was ≤3000 μm). In Protocol AG, visual acuity (VA) was 20/32 to 20/400. In Protocol AH, eyes had a FTMH (≤250 μm at the narrowest point) and VA of 20/25 to 20/400.

Methods: Pneumatic vitreolysis using perfluoropropane (C_3F_8) gas.

Main Outcome Measures: Central VMT release at 24 weeks (Protocol AG) and FTMH closure at 8 weeks (Protocol AH).

Results: From October 2018 through February 2020, 46 participants were enrolled in Protocol AG, and 35 were enrolled in Protocol AH. Higher than expected rates of retinal detachment and tear resulted in early termination of both protocols. Combining studies, 7 of 59 eyes (12% [95% CI, 6%−23%]; 2 eyes in Protocol AG, 5 eyes in Protocol AH) that received PVL developed rhegmatogenous retinal detachment (n = 6) or retinal tear (n = 1). At 24 weeks in Protocol AG, 18 of 23 eyes in the PVL group (78%) versus 2 of 22 eyes in the sham group (9%) achieved central VMT release without rescue vitrectomy (adjusted risk difference, 66% [95% CI, 44%−88%]; $P < 0.001$). The mean change in VA from baseline at 24 weeks was 6.7 letters in the PVL group and 6.1 letters in the sham group (adjusted difference, −0.8 [95% CI, −6.1 to 4.5]; $P = 0.77$). In Protocol AH, 10 of 35 eyes (29% [95% CI, 16%−45%]) achieved FTMH closure without rescue vitrectomy at 8 weeks. The mean change in VA from baseline at 8 weeks was −1.5 letters (95% CI, −10.3 to 7.3 letters).

Conclusions: In most eyes with VMT, PVL induced hyaloid release. In eyes with FTMH, PVL resulted in hole closure in approximately one third of eyes. These studies were terminated early because of safety concerns related to retinal detachments and retinal tears. *Ophthalmology 2021;■:1−12 © 2021 by the American Academy of Ophthalmology*

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Disorders of the vitreoretinal interface represent a spectrum of abnormalities that develop as the posterior hyaloid separates from the internal limiting membrane. Vitreomacular adhesion occurs when the posterior hyaloid remains attached to the internal limiting membrane centrally. Vitreomacular traction (VMT) occurs when vitreomacular adhesion results in tractional distortion of macular architecture with accompanying symptoms,[1] such as decreased central visual acuity (VA) or metamorphopsia. Progression of VMT can lead to a macular hole (MH), in which tractional forces create a full-thickness macular defect with vision loss, frequently requiring surgical intervention.[1]

Treatments for VMT include observation, vitrectomy, and intraocular injection of ocriplasmin. Observation often is recommended because spontaneous resolution occurs in 10% to 30% of cases.[2−10] Vitrectomy may be recommended for severe cases, but it is costly and carries the risk of cataract progression, retinal detachment, and endophthalmitis. Ocriplasmin results in VMT release in 24% to 45% of cases but is used rarely because of the risk of sight-threatening complications and high cost.[4,7,8,11−19]

Vitrectomy with fluid-gas exchange is first-line treatment for most full-thickness MHs (FTMHs) because hole closure rates approach 80% to 100%.[20−25] Disadvantages of

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vitrectomy include high cost, patient discomfort, the need for face-down positioning, and risk of cataract progression, retinal detachment, and endophthalmitis. Ocriplasmin results in MH closure in approximately 60% of cases but is used infrequently because of its cost and risk of sight-threatening complications.[13–18]

Pneumatic vitreolysis is an in-office intraocular injection of an expansile gas to induce release of VMT. In 1995, Chan et al[26] reported VMT release after PVL using perfluoropropane (C_3F_8) gas in 95% of eyes and closure of small stage 2 MHs by release of VMT in 50% of eyes. Subsequent retrospective case series have reported rates of MH closure ranging from 60% to 100%.[27–30] Risks include, but are not limited to, retinal tear, retinal detachment, endophthalmitis, and cataract. To date, no randomized clinical trials have evaluated PVL. If safe and effective, PVL would be a less invasive, lower-cost alternative to vitrectomy. We conducted two multicenter clinical studies to evaluate the safety and efficacy of PVL for symptomatic VMT without an MH (Protocol AG; Fig S1, available at www.aaojournal.org) and with an MH (Protocol AH; Fig S2, available at www.aaojournal.org).

Methods

The DRCR Retina Network conducted a randomized clinical trial (Protocol AG; ClinicalTrials.gov identifier: NCT03647267) to evaluate PVL with C_3F_8 (perfluoropropane) gas injection versus sham injection for treatment of VMT without MH and a single-arm, prospective, observational study (Protocol AH; ClinicalTrials.gov identifier, NCT03677869) to estimate the rate of MH closure after PVL with C_3F_8 gas injection at 28 sites. The studies adhered to the tenets of the Declaration of Helsinki and were approved by The Jaeb Center for Health Research Institutional Review Board. Study participants provided written informed consent. The first participants were enrolled on October 16, 2018, for Protocol AG and November 14, 2018, for Protocol AH. An independent data and safety monitoring committee (DSMC) provided oversight and recommended halting enrollment into both studies on February 11, 2020, after review of the combined data from Protocols AG and AH on the incidence of rhegmatogenous retinal detachments and retinal tears. Follow-up visits continued for enrolled participants and ended on August 6, 2020 for Protocol AG and July 22, 2020 for Protocol AH; results of both protocols are presented with combined safety data.

Protocol AG: Randomized Clinical Trial Assessing the Effects of Pneumatic Vitreolysis on Vitreomacular Traction

Methods

Participants were at least 18 years of age, had central VMT in which the vitreomacular adhesion was 3000 μm or less, had no macular or lamellar hole, and had an electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) VA score of 78 to 24 letters (Snellen equivalent, 20/32−20/400). Presence of VMT was confirmed on OCT by the Duke Reading Center, Durham, NC. Participants were required to avoid high altitude travel and, if phakic, to avoid supine positioning until gas resolution. Prior intraocular injection and vitrectomy were exclusionary. One eye per participant was enrolled.

Randomization schedules were generated by the study statistician using computer-generated random numbers and had a permuted block design (random block sizes of 2 and 4) stratified by site and presence of epiretinal membrane in the central subfield. Study eyes were assigned randomly 1:1 to either PVL or sham injection. Treatment assignments were obtained by clinical personnel on the study website.

Treatment was given on the day of randomization. Follow-up visits occurred at 1, 4, 12, and 24 weeks. At each visit, investigators performed a dilated eye examination, and certified technicians obtained spectral-domain OCT scans and E-ETDRS VA after protocol refraction. Shape discrimination hyperacuity was measured using myVisionTrack (Genentech)[31] at randomization, 12 weeks, and 24 weeks. Participants and technicians were masked to treatment assignment, but investigators were not.

Investigators, who had experience with 10 or more intraocular gas injections, were required to use topical anesthetic, povidone iodine, and a lid speculum for PVL and sham injections. For PVL, 0.3 mL of C_3F_8 was injected into the vitreous with a 30-gauge or smaller needle. For sham injections, the hub of a needleless syringe was pressed against the conjunctival surface to simulate the pressure of an injection. Paracentesis was optional. Investigators used indirect ophthalmoscopy or a VA check to assess for complications. Vitrectomy was permitted after 1 week if VA decreased from baseline ($\geq$10 letters at 1 visit or at least 5 letters at 2 consecutive visits) because of vitreomacular complications and at any time for conditions requiring prompt treatment.

Outcomes. The primary outcome was the proportion of eyes with central VMT release on OCT at 24 weeks without rescue vitrectomy. A sample size of 124 was calculated assuming outcome rates of 30% in the sham group and 60% in the C_3F_8 group, 80% power, 5% type 1 error, and 10% loss to follow-up.

Time to central VMT release without vitrectomy, the proportion of eyes receiving vitrectomy, mean VA change from baseline, and the proportions of eyes gaining or losing 10 letters or more of VA from baseline at 24 weeks were prespecified secondary outcomes. Mean shape discrimination hyperacuity change from baseline and the proportion of eyes without ellipsoid zone integrity (i.e., sections of the ellipsoid zone are missing; graded by central reading center) at 24 weeks were prespecified exploratory outcomes. Safety outcomes included endophthalmitis, retinal tear, retinal detachment, MH development, traumatic cataract, cataract extraction, vitreous hemorrhage, and intraocular pressure events.

Statistical Analysis. In general, binary outcomes were analyzed with logistic regression, continuous outcomes were analyzed with linear regression, and time-to-event outcomes were analyzed with proportional hazards regression. Models for VA, hyperacuity, and ellipsoid zone integrity included the baseline value as a covariate. For time-to-event outcomes, cumulative probabilities were estimated via the Kaplan-Meier method.[32] In logistic regression models, risk difference was estimated using conditional standardization and the delta method.[33] Missing VA or

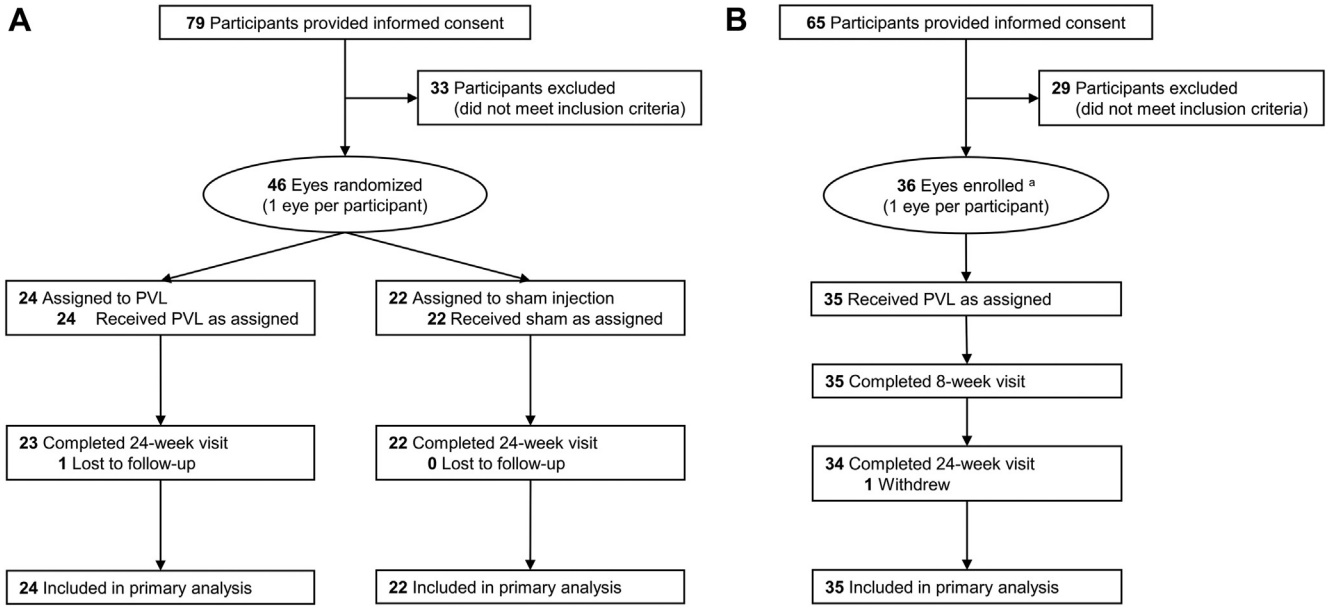

Figure 1. Study flow diagrams. **A**, Randomization and participant flow in Protocol AG. Participants were not screened formally before obtaining informed consent. Reasons for ineligibility were not collected systematically. Visit completion at 24 weeks was prespecified as completion of any study visit from 18 to 40 weeks. **B**, Enrollment and participant flow in Protocol AH. Participants were not screened formally before obtaining informed consent. Reasons for ineligibility were not collected systematically. Visit completion at 24 weeks was prespecified as completion of any study visit from 18 to 40 weeks. [a]One eye that did not have full-thickness macular hole was enrolled, underwent pneumatic vitreolysis (PVL), and completed the 24-week visit, but is not included in any analyses or subsequent levels in the flowchart.

missing central VMT data were imputed by Markov chain Monte Carlo multiple imputation. *P* values less than 0.05 were considered statistically significant. Analyses were conducted with SAS software version 9.4 (SAS Institute).

Results

Study Participants. Forty-six participants, 37% of the recruitment goal of 124, were randomly assigned to PVL (n = 24) or sham (n = 22; Fig 1A). At baseline, mean age was 72 years (standard deviation [SD], 9 years) and 31 (67%) were women (Table 1). Among study eyes, mean VA was 68.5 letters (SD, 9.4 letters; Snellen equivalent, 20/50), 3 eyes (7%) had an epiretinal membrane in the central subfield, and the median length of vitreomacular adhesion in the central subfield was 502 μm (interquartile range, 348−682 μm). Baseline VA letter score, epiretinal membrane, and vitreomacular adhesion length were balanced between groups. Twenty-three participants (96%) in the PVL group and 22 participants (100%) in the sham group completed the 24-week visit.

Central Vitreomacular Traction Release and Rescue Vitrectomy. At 24 weeks, the number of eyes with central VMT release without rescue vitrectomy (primary outcome) in the PVL group was 18 of 23 (78%) versus 2 of 22 (9%) in the sham group (adjusted risk difference, 66% [95% CI, 44%−88%]; $P < 0.001$; Table 2; Fig 2). Rescue vitrectomy was performed before central VMT release in 1 of 23 eyes (4%) in the PVL group (to treat MH) and 0 of 22 eyes in the sham group (risk difference, 4% [95% CI, −4% to 13%]; $P = 0.31$). Two eyes in the PVL group underwent vitrectomy after VMT release to treat retinal detachment. Tabulations of the primary outcome by baseline characteristics are shown in Table S1 (available at www.aaojournal.org); however, the small sample size precluded subgroup analyses.

Secondary Outcome: Visual Acuity. The mean VA change from baseline to 24 weeks was 6.7 letters (SD, 12.4 letters) in the PVL group (n = 23) and 6.1 letters (SD, 9.6 letters) in the sham group (n = 22; adjusted difference, −0.8 [95% CI, −6.1 to 4.5]; $P = 0.77$; negative values indicate greater improvement in the sham group after adjustment for baseline VA; Table 2; Fig 3; Fig S3, available at www.aaojournal.org); 8 eyes (35%) in the PVL group and 7 eyes (32%) in the sham group gained 10 letters or more (adjusted risk difference, −10% [95% CI, −48% to 29%]; $P = 0.63$); 1 eye (4%) in the PVL group and 0 eyes in the sham group lost 10 letters or more (risk difference, 4% [95% CI, −11% to 21%]; $P = 0.53$).

Exploratory Outcomes. The mean shape discrimination hyperacuity change from baseline to 24 weeks was −0.12 logarithm of the minimum angle of resolution (logMAR; SD, 0.22 logMAR) in the PVL group (n = 19) and −0.06 logMAR (SD, 0.20 logMAR) in the sham group (n = 21; adjusted mean difference, −0.09 [95% CI, −0.21 to 0.02]; $P = 0.12$; Table 2; Fig S4, available at www.aaojournal.org). Loss of ellipsoid zone integrity in the central subfield at 24 weeks was found in 6 of 22 eyes in the PVL group (27%) and in 11 of 22 eyes in the sham group (50%; adjusted difference, −52% [95% CI, −91% to −13%]; $P = 0.009$).

Table 1. Baseline Characteristics in Protocol AG and Protocol AH

Characteristic	Protocol AG		Protocol AH
	Pneumatic Vitreolysis (n = 24)	*Sham (n = 22)*	*Pneumatic Vitreolysis (n = 35)*
Participant characteristics			
Age, yrs	70 ± 10	75 ± 8	69 ± 9
Sex			
Female	15 (63)	16 (73)	24 (69)
Male	9 (38)	6 (27)	11 (31)
Race or ethnicity			
White (non-Hispanic)	16 (67)	17 (77)	27 (77)
Hispanic or Latino	4 (17)	5 (23)	5 (14)
Black or African American (non-Hispanic)	3 (13)	0	3 (9)
Unknown or not reported	1 (4)	0	0
Diabetes			
No	16 (67)	12 (55)	27 (77)
Type 2	8 (33)	10 (45)	8 (23)
Ocular characteristics			
Visual acuity letter score			
Mean ± SD	67.8 ± 10.3	69.2 ± 8.4	55.8 ± 14.0
Mean Snellen equivalent	20/50	20/40	20/80
20/25 or better (79 letters or more)	0	0	2 (6)
20/32–20/40 (78–69 letters)	15 (63)	16 (73)	2 (6)
20/50–20/80 (68–54 letters)	6 (25)	4 (18)	20 (57)
20/100–20/160 (53–39 letters)	3 (13)	2 (9)	6 (17)
20/200–20/400 (38–19 letters)	0	0	5 (14)
Shape discrimination hyperacuity, logMAR			
Mean ± SD	0.32 ± 0.27	0.38 ± 0.27	NA
Mean Snellen equivalent	20/40	20/50	NA
Intraocular pressure	15 ± 4	14 ± 3	16 ± 3
Lens status			
Phakic	14 (58)	9 (41)	28 (80)
Posterior chamber intraocular lens	10 (42)	13 (59)	7 (20)
Lattice degeneration	2 (8)	0	3 (9)
Prior treatment for retinal tear	0	0	0
Atrophic retinal hole	0	0	0
Epiretinal membrane in central subfield (randomization stratification factor)*	2 (8)	1 (5)	1 (3)
Width of vitreomacular attachment that extends within the central subfield, μm*	480 (315–694)	503 (427–646)	325 (185–496)†
Macular hole width at narrowest point, μm*	NA	NA	79 (39–111)
Vitreopapillary traction at the optic nerve*	2 (8)	3 (14)	0
Loss of ellipsoid zone integrity in central subfield*	15 (63)	8 (36)	35 (100)
Loss of ellipsoid zone integrity in foveal center*	11 (46)	8 (36)	35 (100)

logMAR = logarithm of the minimum angle of resolution; NA = not applicable; SD = standard deviation.
Data are presented as no. (%), mean ± SD, or median (interquartile range).
*Graded by central reading center.
†Unavailable for 1 eye in which vitreomacular traction did not extend into the central subfield.

Protocol AH: Single-Arm Study Assessing the Effects of Pneumatic Vitreolysis on Macular Hole

Methods

Participants were at least 18 years of age, had central VMT in which the vitreomacular adhesion was 3000 μm or less, FTMH of 250 μm or less at the narrowest point, and E-ETDRS VA score of 78 to 19 letters (Snellen equivalent, 20/25–20/400). Presence of VMT and MH were confirmed on OCT by the reading center. Participants had to avoid high-altitude travel and, if phakic, avoid supine positioning until gas resolution. Prior intraocular injection and vitrectomy were exclusionary. One eye per participant was enrolled.

Treatment was administered at enrollment. Follow-up visits occurred at 1, 4, 8, and 24 weeks. At each visit, investigators performed a dilated eye examination, and certified technicians obtained OCT and E-ETDRS VA following protocol refraction.

The gas injection procedure was identical to that used in Protocol AG. Participants were required to position face-down for 50% of the time for at least 4 days after the injection. Rescue vitrectomy was permitted between 4 and 8 weeks if the size of the MH did not improve after PVL; thereafter, vitrectomy could be performed at investigator discretion. Vitrectomy was permitted at any time for a condition requiring prompt intervention.

Outcomes. The primary outcome was the proportion of eyes with MH closure of the inner retinal layers at 8 weeks

Table 2. Primary, Secondary, and Exploratory Efficacy Outcomes at 24 Weeks in Protocol AG

Outcome	Pneumatic Vitreolysis (n = 23)[#]	Sham (n = 22)[#]	Difference, % (95% Confidence Interval)[*]	*P* Value[*]
Primary outcome				
Proportion of eyes with central VMT release without rescue vitrectomy	18 (78)	2 (9)	66 (44 to 88)	< 0.001
Secondary outcomes				
Rescue vitrectomy before the 24-wk visit	1 (4)	0	4 (−4 to 13)	0.31
Rescue vitrectomy before 24 wks or planned at the 24-wk visit	1 (4)	1 (5)	NA	NA
Central VMT status				
Released without rescue vitrectomy	18 (78)	2 (9)	NA	NA
Released with rescue vitrectomy	1 (4)	0	NA	NA
Not released and no rescue vitrectomy	4 (17)	20 (91)	NA	NA
Not released despite rescue vitrectomy	0	0	NA	NA
Visual acuity letter score				
Mean ± SD	73.0 ± 16.4	75.3 ± 6.1	NA	NA
Mean Snellen equivalent	20/40	20/32	NA	NA
Visual acuity letter score change from baseline[†]				
Mean ± SD	6.7 ± 12.4	6.1 ± 9.6	−0.8 (−6.1 to 4.5)	0.77
≥10-letter gain	8 (35)	7 (32)	−10 (−48 to 29)	0.63
≥10-letter loss	1 (4)[‡]	0	4 (−11 to 21)[§]	0.53[§]
Exploratory outcomes				
Shape discrimination hyperacuity, logMAR[‖]	0.16 ± 0.23 (n = 19)	0.30 ± 0.27 (n = 21)	NA	NA
Mean Snellen equivalent[‖]	20/32 (n = 19)	20/50 (n = 21)	NA	NA
Change in shape discrimination hyperacuity from baseline, logMAR[‖]	−0.12 ± 0.22 (n = 19)	−0.06 ± 0.20 (n = 21)	−0.09 (−0.21 to 0.02)	0.12
Loss of ellipsoid zone integrity in central subfield[†]	6 (27) (n = 22)	11 (50)	−52 (−91 to −13)	0.009
Loss of ellipsoid zone integrity in foveal center[†]	4 (18) (n = 22)	8 (36)	−22 (−50 to 5)	0.10

logMAR = logarithm of the minimum angle of resolution; NA = not analyzed; PVL = pneumatic vitreolysis; SD = standard deviation; VMT = vitreomacular traction.

*For the primary and secondary visual acuity outcomes, missing data were imputed by Markov chain Monte Carlo multiple imputation with 100 imputations. Outcomes related to visual acuity, shape discrimination hyperacuity, and loss of ellipsoid zone integrity were adjusted for baseline visual acuity, shape discrimination hyperacuity, and ellipsoid zone integrity, respectively. The difference column is the difference between the PVL and sham groups; positive differences indicate a larger value in the PVL group, and negative values indicate a larger value in the sham group. Summary statistics and sample size are based on participants completing the 24-week visit without imputation of missing data.

†Per the statistical analysis plan, values of less than 3 SDs more or less than the overall mean were truncated. This applied to one eye in the PVL group that showed a loss of 65 letters, which was truncated at −36.2 letters (3 SDs less than the overall mean).

‡Reason for vision loss was cataract.

§Because of event rate of 0% in the sham group, the risk difference was calculated using the Newcombe method,[34,35] and the *P* value was calculated using Barnard's exact unconditional test without imputation of missing data.

‖Lower values indicate better hyperacuity.

#Values shown are mean ± SD or no. (%).

without rescue vitrectomy. The sample size of 50 was chosen for convenience. Time to MH closure without vitrectomy, time to central VMT release without vitrectomy, proportion of eyes receiving vitrectomy, mean VA change from baseline, and the proportions of eyes gaining or losing 10 letters or more of VA from baseline at 8 and 24 weeks were prespecified secondary outcomes. The proportion of eyes with MH closure of the inner retinal layers with outer retinal lucency without vitrectomy and the proportion of eyes without ellipsoid zone integrity, as determined by the reading center, at 8 and 24 weeks were prespecified exploratory outcomes. Key safety outcomes were the same as protocol AG except progression to MH.

Statistical Analysis. Confidence intervals for proportions were estimated with the Wilson method.[36,37] Missing MH and VA data were imputed by Markov chain Monte Carlo multiple imputation.

Results

Study Participants. Thirty-five eligible participants were enrolled (Fig 1B). Mean age was 69 years (SD, 9 years), and 24 patients (69%) were women (Table 1). Among study eyes, mean VA was 55.8 letters (SD, 14.0 letters; Snellen equivalent, 20/80), 1 eye (3%) had an epiretinal membrane in the central subfield, and median MH width at the narrowest point was 79 μm (interquartile range, 39—111 μm). All 35 participants (100%) completed the 8-week visit, and 34 (97%) completed the 24-week visit.

Macular Hole Closure and Rescue Vitrectomy. At 8 weeks, MH closure of the inner retinal layers without rescue vitrectomy (primary outcome) occurred in 10 of 35 eyes (29%; 95% CI, 16%—45%); rescue vitrectomy was performed in 12 eyes (34%; 95% CI, 21%—51%) and was successful in 10 eyes (Table 3). Through 24 weeks, MH

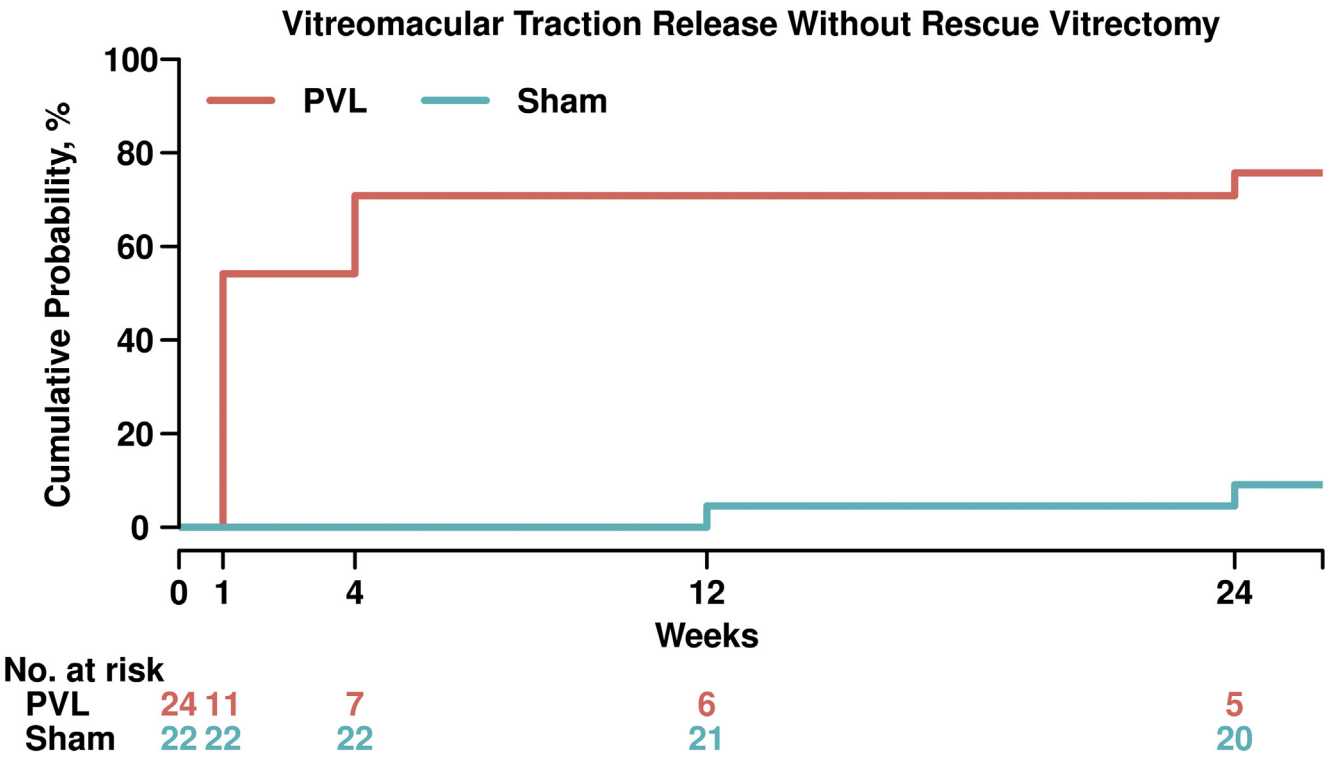

Figure 2. Graph showing time to central vitreomacular traction release without rescue vitrectomy through 24 weeks by treatment group in Protocol AG. The cumulative probability of central vitreomacular traction release without rescue vitrectomy at 24 weeks was 76% (95% CI, 57%–90%) in the pneumatic vitreolysis (PVL) group and 9% (95% CI, 2%–32%) in the sham group (hazard ratio, 19.06 [95% CI, 4.64–78.30]; $P < 0.001$).

closure was achieved without vitrectomy in 10 of 35 eyes (29%; 95% CI, 17%–47%; Fig 4). Among eyes completing the 24-week visit, rescue vitrectomy was performed in 23 of 34 eyes (68%; 95% CI, 51%–81%); 1 eye that did not complete the 24-week visit underwent vitrectomy within 24 weeks of randomization. Primary indications for vitrectomy were MH (21 procedures in 20 eyes) and rhegmatogenous retinal detachment (5 procedures in 4 eyes). Subgroup analyses of the primary outcome are shown in Table S2 (available at www.aaojournal.org).

Secondary Outcomes. Through 24 weeks, central VMT released without vitrectomy in 33 of 35 eyes (94%; 95% CI, 83%–99%; Fig 5). Among 35 eyes at 8 weeks, the mean VA change from baseline was −1.5 letters (95% CI, −10.3 to 7.3 letters), 12 eyes (34%; 95% CI, 21%–51%) gained 10 letters or more, and 8 eyes (23%; 95% CI, 12%–39%) lost 10 letters or more (Table 3; Fig S5, available at www.aaojournal.org). Among 34 eyes at 24 weeks, the mean VA change from baseline was 9.2 letters (95% CI, 4.3–14.4 letters), 18 eyes (53%; 95% CI, 37%–69%) gained 10 letters or more, and 3 eyes (9%; 95% CI, 3%–23%) lost 10 letters or more.

Exploratory Outcomes. Macular hole inner retinal layers closed with a residual outer retinal lucency without rescue vitrectomy in 4 of 31 eyes (13%; 95% CI, 5%–29%) at 8 weeks and 6 of 34 eyes (18%; 95% CI, 8%–34%) at 24 weeks (Table 3). Loss of ellipsoid zone integrity in the central subfield was found in 29 of 31 eyes (94%; 95% CI, 79%–98%) at 8 weeks and in 25 of 34 eyes (74%; 95% CI, 57%–85%) at 24 weeks.

Combined Safety Findings from Both Protocols

Considering all eyes that underwent PVL in either Protocol AG (n = 24) or Protocol AH (n = 35), 7 of 59 eyes (12%; 95% CI, 6%–23%) had a rhegmatogenous retinal detachment or retinal tear (6 detachments and 1 tear without detachment), including 2 of 24 eyes in the PVL group in Protocol AG (8%) and 5 of 35 eyes in Protocol AH (14%); all were treated with vitrectomy (Table 4; Table S3, available at www.aaojournal.org). Rates of retinal detachment or tear by baseline factors in the PVL groups from Protocol AG and Protocol AH are shown in Table S4 (available at www.aaojournal.org). No cases of retinal detachment or tear occurred in the sham group in Protocol AG. Among phakic eyes at baseline, cataract surgery was performed in 1 of 14 eyes (7%) in the PVL group in Protocol AG (for traumatic cataract resulting from the preinjection paracentesis), in 0 of 9 eyes in the sham group in Protocol AG, and in 2 of 28 eyes (7%) in Protocol AH. No study eyes developed endophthalmitis. No deaths occurred.

Discussion

These studies showed that PVL was effective for inducing VMT release, but less effective for closing MH, and had

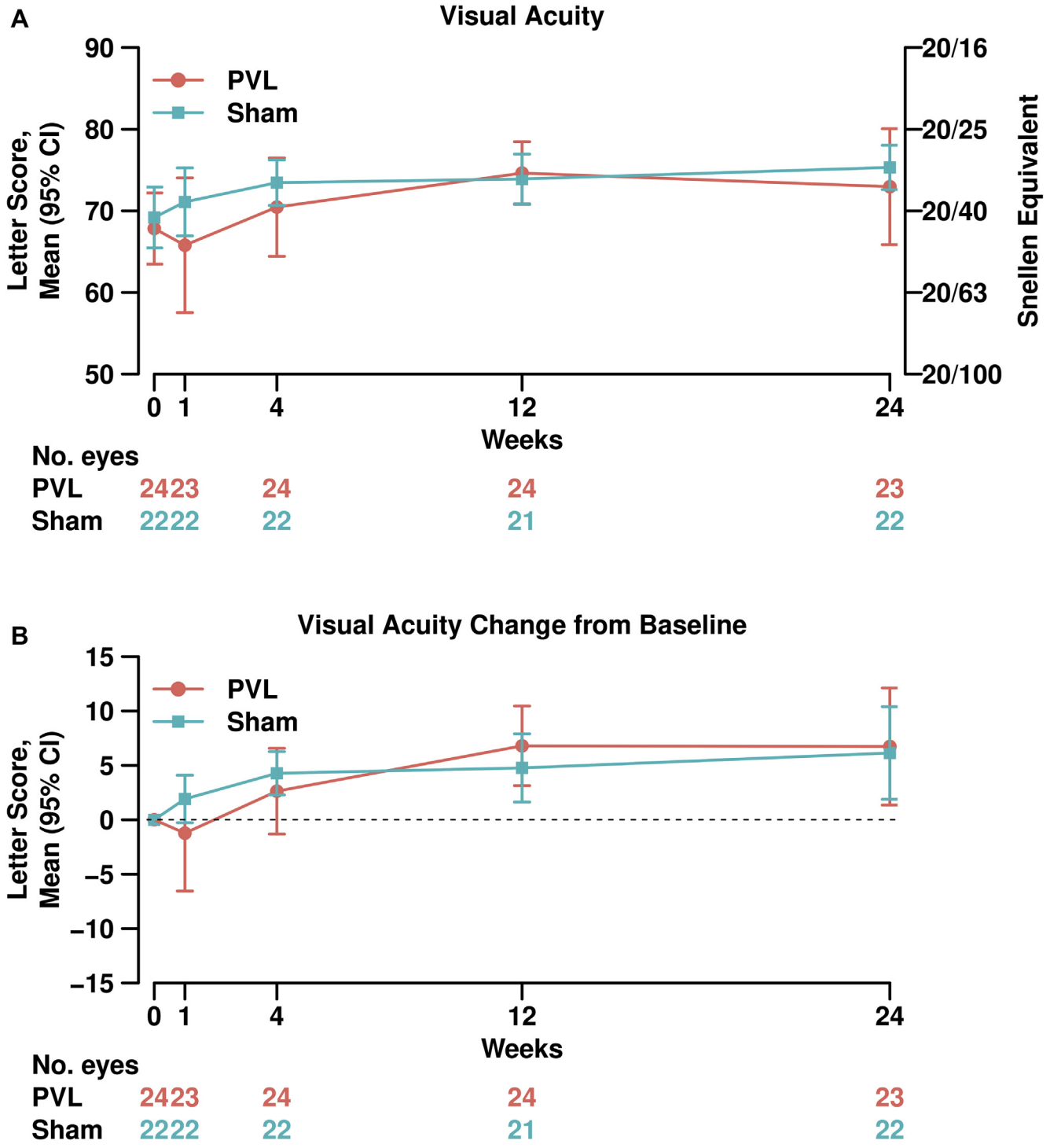

Figure 3. Graphs showing visual acuity and change in visual acuity through 24 weeks by treatment group in Protocol AG: (**A**) visual acuity letter score and (**B**) visual acuity letter score change from baseline. Orange circles and blue squares represent the mean for the pneumatic vitreolysis (PVL) and sham groups, respectively, and error bars represent 95% confidence intervals (CIs). The number of eyes contributing data at each visit is given below the graphs.

higher than expected rates of retinal detachments and tears, which led to early discontinuation of the studies. The VMT release rate in Protocol AG was consistent with that in previous uncontrolled studies, but no significant difference was found in central VA or shape discrimination hyperacuity between the PVL and sham groups at 24 weeks. The improved VA in sham eyes without MH in Protocol AG highlights the favorable natural history of VMT without

Table 3. Primary, Secondary, and Exploratory Efficacy Outcomes at 8 and 24 Weeks in Protocol AH

Outcome	Pneumatic Vitreolysis*	95% Confidence Interval*
8 wks	n = 35	
Primary outcome		
Proportion of eyes with macular hole closure of the inner retinal layers without rescue vitrectomy	10 (29)	16–45
Secondary outcomes		
Rescue vitrectomy before the 8-wk visit	12 (34)	21%–51%
Macular hole status		
Closure without rescue vitrectomy	10 (29)	NA
Closure with rescue vitrectomy	10 (29)	NA
No closure and no rescue vitrectomy	13 (37)	NA
No closure despite rescue vitrectomy	2 (6)	NA
Visual acuity letter score		NA
Mean ± SD	54.2 ± 23.8	NA
Mean Snellen equivalent	20/80	NA
Median (IQR)	61.0 (71.0–42.0)	NA
Median Snellen equivalent	20/63	NA
Change in visual acuity letter score from baseline		
Mean ± SD	−1.5 ± 25.6	−10.3 to 7.3
Median (IQR)	3.0 (−9.0 to 13.0)	NA
≥10-letter gain	12 (34)	21%–51%
≥10-letter loss	8 (23)	12%–39%
Exploratory outcomes		
Macular hole closure of the inner retinal layers with outer retinal lucency without rescue vitrectomy	4 (13) (n = 31)†,‡	5%–29%
Loss of ellipsoid zone integrity in central subfield	29 (94) (n = 31)†,‡	79%–98%
Loss of ellipsoid zone integrity in foveal center	28 (88) (n = 32)†	72%–95%
24 wks	n = 34	
Secondary outcomes		
Rescue vitrectomy before the 24-wk visit§	23 (68)	51–81
Rescue vitrectomy before or planned at the 24-wk visit	24 (71)	NA
Macular hole status		
closure without rescue vitrectomy	10 (29)	NA
closure with rescue vitrectomy	22 (65)	NA
No closure and no rescue vitrectomy	1 (3)	NA
No closure despite rescue vitrectomy	1 (3)	NA
Visual acuity letter score		
Mean ± SD	66.0 ± 16.5	NA
Mean Snellen equivalent	20/50	NA
Median (IQR)	68.0 (76.0–56.0)	NA
Median Snellen equivalent	20/50	NA
Change in visual acuity letter score from baseline		
Mean ± SD	9.2 ± 14.5	4.3–14.4
Median (IQR)	10.0 (3.0–15.0)	NA
≥10-letter gain	18 (53)	37%–69%
≥10-letter loss	3 (9)‖	3%–22%
Exploratory outcomes		
Macular hole closure of the inner retinal layers with outer retinal lucency without rescue vitrectomy	6 (18)	8%–34%
Loss of ellipsoid zone integrity in central subfield	25 (74)	57%–85%
Loss of ellipsoid zone integrity in foveal center	18 (53)	37%–69%

IQR = interquartile range; NA = not analyzed; PVL = pneumatic vitreolysis; SD = standard deviation.
Data are no. (%), unless otherwise indicated.
*Summary statistics include participants completing the corresponding visit without imputation of missing data. For secondary visual acuity outcomes, missing data were imputed by Markov chain Monte Carlo multiple imputation (100 imputations).
†OCT not performed in 3 patients; 2 had no view because of retinal detachment and 1 had recent vitrectomy for macular hole.
‡OCT ungradable in 1 patient.
§One eye that missed the 24-week visit underwent vitrectomy for macular hole within 24 weeks of randomization.
‖Reasons for vision loss were retinal detachment, after vitrectomy to repair macular hole, and unknown.

MH. Regression to the mean also may explain VA gains observed in sham eyes. In eyes without MH in Protocol AG, PVL resulted in greater rates of intact OCT ellipsoid zone compared with sham treatment. In almost all eyes with MH, PVL resulted in hyaloid release, but the MH closed without vitrectomy only in 29% of eyes. This rate is

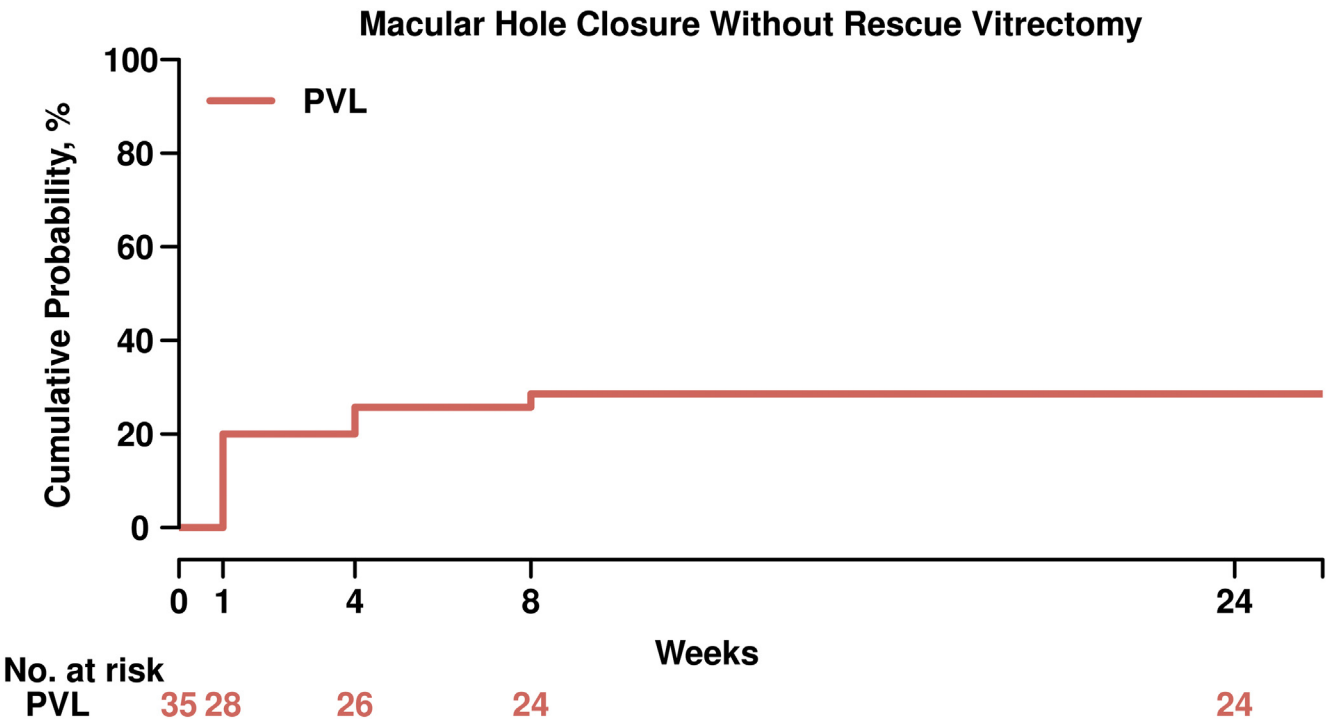

Figure 4. Graph showing time to macular hole closure without rescue vitrectomy through 24 weeks in Protocol AH. The cumulative probability of macular hole closure without rescue vitrectomy through 24 weeks was 29% (95% CI, 17%–47%). PVL = pneumatic vitreolysis.

disappointing compared with the nearly 80% to 100% MH closure rate of vitrectomy,[20–25] especially because our cohort consisted of small MHs that almost always close with surgery.

Pneumatic vitreolysis was associated with more complications than expected when designing the study. After 62 participants enrolled in the two studies, the DSMC noted the rate of retinal tear or detachment was more than the estimate

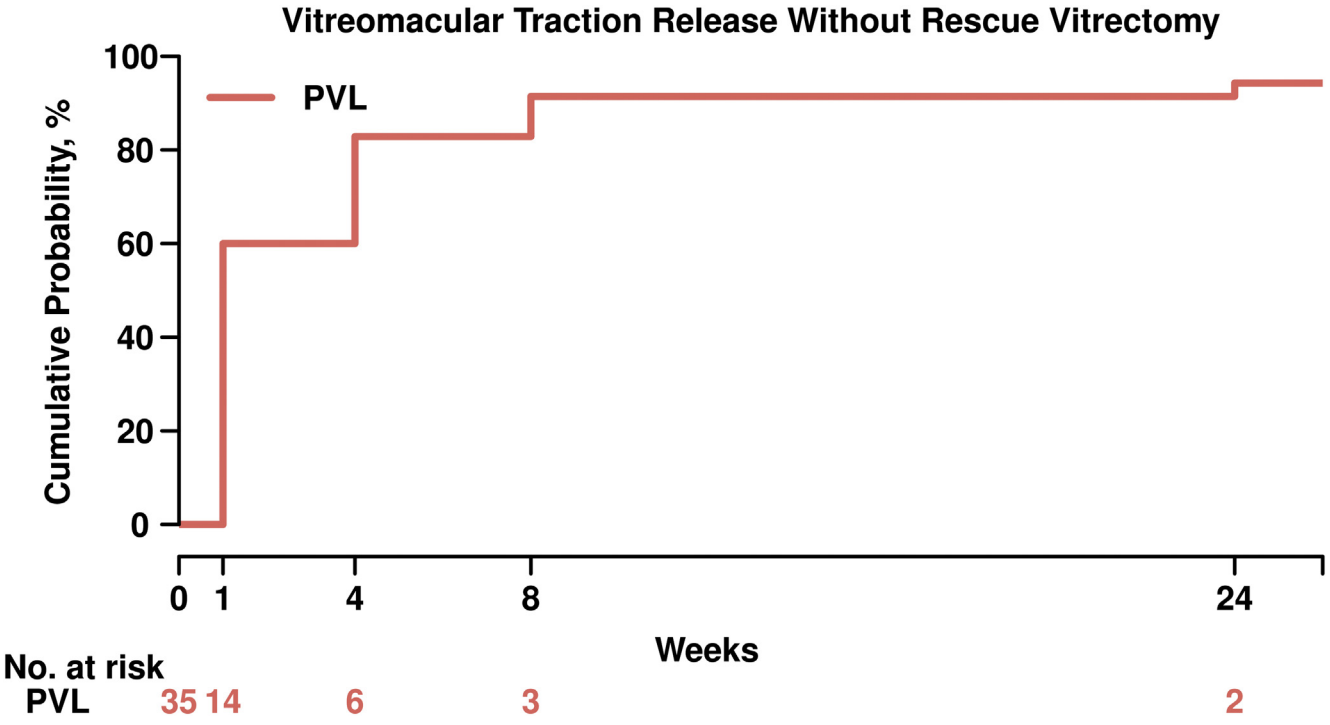

Figure 5. Graph showing time to vitreomacular traction release without rescue vitrectomy through 24 weeks in Protocol AH. The cumulative probability of central vitreomacular traction release without rescue vitrectomy through 24 weeks was 94% (95% CI, 83%–99%). PVL = pneumatic vitreolysis.

Table 4. Safety Outcomes through 24 Weeks by Group in Protocols AG and AH

Event	Protocol AG			Protocol AH		Combined	
	Pneumatic Vitreolysis (n = 24)	*Sham (n = 22)*	*P Value*	*Pneumatic Vitreolysis (n = 35)*	*95% Confidence Interval*	*Pneumatic Vitreolysis (n = 59)*	*95% Confidence Interval*
Ocular safety outcomes in study eyes							
Endophthalmitis	0	0	NA	0	0–10	0	0–6
Retinal detachment or retinal tear	2 (8)*	0	NA	5 (14)*	6–29	7 (12)	6–23
Rhegmatogenous retinal detachment	2 (8)	0	0.22	4 (11)	5–26	6 (10)	5–20
Retinal tear without detachment	0	0	Undefined	1 (3)	1–15	1 (2)	0–9
Vitreous hemorrhage	1 (4)	0	0.51	1 (3)	1–15	2 (3)	1–12
Macular hole†	1 (4)*	1 (5)	1.00	NA	NA	NA	NA
Adverse intraocular pressure event	2 (8)‡	2 (9)‡	1.00	7 (20)‡	10–36	9 (15)	8–27
Intraocular pressure increase ≥ 10 mmHg from baseline	1 (4)	2 (9)	NA	2 (6)	NA	3 (5)	NA
Intraocular pressure ≥ 30 mmHg	0	0	NA	2 (6)	NA	2 (3)	NA
Initiation of medication to lower intraocular pressure	2 (8)	0	NA	7 (20)	NA	9 (15)	NA
Glaucoma procedure	0	0	NA	0	NA	0	NA
Traumatic cataract§	1 (7) (n = 14)‖	0 (n = 9)	NA	0 (n = 28)	0–12	1 (2) (n = 42)	0–12
Cataract extraction§	1 (7) (n = 14)	0 (n = 9)	0.56	2 (7) (n = 28)	2–23	3 (7) (n = 42)	2–19
Systemic safety outcomes							
Death	0	0	Undefined	0	0–10	0	0–6
Serious systemic adverse event	1 (4)	0	0.51	4 (11)	5–26	5 (8)	4–18

NA = not analyzed
*Treated with vitrectomy.
†Detected on clinical examination or OCT.
‡Paracentesis was performed before injection in the pneumatic vitreolysis groups but not the sham group.
§Limited to eyes that were phakic at baseline.
‖Initially diagnosed as endophthalmitis but later determined to be traumatic cataract caused by paracentesis.

in the informed consent form (1%), an estimate derived from studies of ocriplasmin for VMT. The DSMC recommended suspension of enrollment and for the study group to review these cases, to inform investigators, and to revise the informed consent form.[4,8] The informed consent form and protocol were revised to include a retinal detachment incidence range of 5% to 13% based on prior PVL and pneumatic retinopexy studies. In the largest prior study of PVL for VMT with and without an MH, 4 of 80 eyes (5%) developed a retinal tear or detachment; in studies of pneumatic retinopexy to repair retinal detachment using C_3F_8 or SF_6 (sulfur hexafluoride) gas injection, the percentage of recurrent retinal detachment or new tears ranged from 15% to 23%.[38–42] After resumption of enrollment, additional retinal tears and detachments occurred, bringing the combined total from both studies to 7 of the 59 eyes that received the gas injection (12%; 95% CI, 6%–23%), and the DSMC recommended termination of recruitment. It is unclear why the combined rate of retinal detachment and tear in protocols AG and AH was higher than in previous studies of PVL for VMT.

Most of the retinal tears and detachments in these two studies occurred in eyes with MHs (Protocol AH). Although VMT and MH are considered part of the same spectrum of diseases caused by VMT, they are clinically different entities. A difference in risk for retinal detachment could exist between these conditions, as well as a difference in indication for PVL. It is unknown if modifications to the injection procedure would have resulted in a lower risk for retinal detachment and tear. Anecdotal observations suggest that gas injection at the highest point of the globe and avoidance of so-called fish-egg bubbles may reduce vitreoretinal complications. Despite the higher than expected rate of retinal tears and detachment, some patients and physicians may still consider PVL for the treatment of VMT and MH. This study is too small to make definitive statements as to whether PVL should be performed.

These studies have limitations. First, the planned sample sizes were not met because of early termination, and the original sample size calculations were based on anatomic, not visual, outcomes; thus, our power to detect modest differences between treatment groups (Protocol AG) and the precision of estimated rates (Protocol AH) were relatively low. Second, follow-up ended after 24 weeks, so data on long-term outcomes are unavailable.

In conclusion, in most eyes with VMT, PVL induced hyaloid release. In eyes with MH, PVL resulted in MH closure in approximately one third of eyes. These studies were terminated early because of safety concerns related to retinal detachments and retinal tears.

Footnotes and Disclosures

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*Members of the DRCR Retina Network that participated in this trial are available online at www.aaojournal.org.

HUMAN SUBJECTS: Human subjects were included in this study. The studies adhered to the tenets of the Declaration of Helsinki and were approved by a central institutional review board. Study participants provided written informed consent.

No animal subjects were included in this study.

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Abbreviations and Acronyms:
C_3F_8 = perfluoropropane; **DSMC** = data and safety monitoring committee; **E-ETDRS** = Electronic Early Treatment Diabetic Retinopathy Study; **FTMH** = full-thickness macular hole; **logMAR** = logarithm of the minimum angle of resolution; **MH** = macular hole; **PVL** = pneumatic vitreolysis; **SD** = standard deviation; **VA** = visual acuity; **VMT** = vitreomacular traction.

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C_3F_8, DRCR Retina Network, Pneumatic vitreolysis, Vitreomacular traction macular hole.

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References

1. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology*. 2013;120(12):2611−2619.
2. Almeida DR, Chin EK. Spontaneous resolution of vitreomacular traction in two patients with diabetic macular edema. *Case Rep Ophthalmol*. 2014;5(1):66−71.
3. Dimopoulos S, Bartz-Schmidt KU, Gelisken F, et al. Rate and timing of spontaneous resolution in a vitreomacular traction group: should the role of watchful waiting be re-evaluated as an alternative to ocriplasmin therapy? *Br J Ophthalmol*. 2015;99(3):350−353.
4. Dugel PU, Tolentino M, Feiner L, et al. Results of the 2-year Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) randomized trial. *Ophthalmology*. 2016;123(10):2232−2247.
5. Hwang DJ, Park KH, Woo SJ. Spontaneous resolution of vitreomacular traction syndrome with persistent vitreofoveal adhesion observed on spectral-domain optical coherence tomography. *Can J Ophthalmol*. 2012;47(5):e17−e19.
6. John VJ, Flynn Jr HW, Smiddy WE, et al. Clinical course of vitreomacular adhesion managed by initial observation. *Retina*. 2014;34(3):442−446.
7. Neffendorf JE, Kirthi V, Pringle E, Jackson TL. Ocriplasmin for symptomatic vitreomacular adhesion. *Cochrane Database Syst Rev*. 2017;10:CD011874.
8. Stalmans P, Benz MS, Gandorfer A, et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. *N Engl J Med*. 2012;367(7):606−615.
9. Theodossiadis GP, Grigoropoulos VG, Theodoropoulou S, et al. Spontaneous resolution of vitreomacular traction demonstrated by spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2014;157(4):842−851 e841.

10. Tzu JH, John VJ, Flynn Jr HW, et al. Clinical course of vitreomacular traction managed initially by observation. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(5):571–576.
11. Lim J, Glassman A, Aiello L, et al. Macula Society collaborative retrospective study of ocriplasmin for symptomatic vitreomacular adhesion. *Ophthalmol Retina*. 2017;1(5):413–420.
12. Stefanini FR, Maia M, Falabella P, et al. Profile of ocriplasmin and its potential in the treatment of vitreomacular adhesion. *Clin Ophthalmol*. 2014;8:847–856.
13. Stone TW, ed. *ASRS 2018 Preference and Trends Membership Survey*. Chicago, IL: American Society of Retina Specialists; 2018.
14. Fahim AT, Khan NW, Johnson MW. Acute panretinal structural and functional abnormalities after intravitreous ocriplasmin injection. *JAMA Ophthalmol*. 2014;132(4):484–486.
15. Freund KB, Shah SA, Shah VP. Correlation of transient vision loss with outer retinal disruption following intravitreal ocriplasmin. *Eye (Lond)*. 2013;27(6):773–774.
16. Hager A, Seibel I, Riechardt A, et al. Does ocriplasmin affect the RPE-photoreceptor adhesion in macular holes? *Br J Ophthalmol*. 2015;99(5):635–638.
17. Kim JE. Safety and complications of ocriplasmin: ocriplasmin, ocriplasmin; oh, how safe art thou? *JAMA Ophthalmol*. 2014;132(4):379–380.
18. Tibbetts MD, Reichel E, Witkin AJ. Vision loss after intravitreal ocriplasmin: correlation of spectral-domain optical coherence tomography and electroretinography. *JAMA Ophthalmol*. 2014;132(4):487–490.
19. Chang JS, Smiddy WE. Cost evaluation of surgical and pharmaceutical options in treatment for vitreomacular adhesions and macular holes. *Ophthalmology*. 2014;121(9):1720–1726.
20. Kim JW, Freeman WR, Azen SP, et al. Prospective randomized trial of vitrectomy or observation for stage 2 macular holes. Vitrectomy for Macular Hole Study Group. *Am J Ophthalmol*. 1996;121(6):605–614.
21. Parravano M, Giansanti F, Eandi CM, et al. Vitrectomy for idiopathic macular hole. *Cochrane Database Syst Rev*. 2015;5:CD009080.
22. Rao P, Yonekawa Y, Abbey A, et al. Prevalence and surgical outcomes of macular hole in eyes with age-related macular degeneration. *Ophthalmol Retina*. 2017;1(2):158–164.
23. Kumagai K, Furukawa M, Ogino N, et al. Vitreous surgery with and without internal limiting membrane peeling for macular hole repair. *Retina*. 2004;24(5):721–727.
24. Spiteri Cornish K, Lois N, Scott NW, et al. Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. *Ophthalmology*. 2014;121(3):649–655.
25. Tadayoni R, Gaudric A, Haouchine B, Massin P. Relationship between macular hole size and the potential benefit of internal limiting membrane peeling. *Br J Ophthalmol*. 2006;90(10):1239–1241.
26. Chan CK, Wessels IF, Friedrichsen EJ. Treatment of idiopathic macular holes by induced posterior vitreous detachment. *Ophthalmology*. 1995;102(5):757–767.
27. Costa RA, Cardillo JA, Morales PH, et al. Optical coherence tomography evaluation of idiopathic macular hole treatment by gas-assisted posterior vitreous detachment. *Am J Ophthalmol*. 2001;132(2):264–266.
28. Jorge R, Costa RA, Cardillo JA, et al. Optical coherence tomography evaluation of idiopathic macular hole treatment by gas-assisted posterior vitreous detachment. *Am J Ophthalmol*. 2006;142(5):869–871.
29. Rodrigues IA, Stangos AN, McHugh DA, Jackson TL. Intravitreal injection of expansile perfluoropropane (c(3)f(8)) for the treatment of vitreomacular traction. *Am J Ophthalmol*. 2013;155(2):270–276 e272.
30. Steinle NC, Dhoot DS, Quezada Ruiz C, et al. Treatment of vitreomacular traction with intravitreal perfluoropropane (C3f8) injection. *Retina*. 2017;37(4):643–650.
31. Wang YZ, He YG, Mitzel G, et al. Handheld shape discrimination hyperacuity test on a mobile device for remote monitoring of visual function in maculopathy. *Invest Ophthalmol Vis Sci*. 2013;54(8):5497–5505.
32. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457–481.
33. Localio AR, Margolis DJ, Berlin JA. Relative risks and confidence intervals were easily computed indirectly from multivariable logistic regression. *J Clin Epidemiol*. 2007;60(9):874–882.
34. Fagerland MW, Lydersen S, Laake P. Recommended confidence intervals for two independent binomial proportions. *Stat Methods Med Res*. 2015;24(2):224–254.
35. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873–890.
36. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927;22(158):209–212.
37. Lott A, Reiter JP. Wilson confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data. *Am Stat*. 2020;74(2):109–115.
38. Chan CK, Lin SG, Nuthi AS, Salib DM. Pneumatic retinopexy for the repair of retinal detachments: a comprehensive review (1986–2007). *Surv Ophthalmol*. 2008;53(5):443–478.
39. Tornambe PE. Pneumatic retinopexy: the evolution of case selection and surgical technique. A twelve-year study of 302 eyes. *Trans Am Ophthalmol Soc*. 1997;95:551–578.
40. Poliner LS, Grand MG, Schoch LH, et al. New retinal detachment after pneumatic retinopexy. *Ophthalmology*. 1987;94(4):315–318.
41. Chen JC, Robertson JE, Coonan P, et al. Results and complications of pneumatic retinopexy. *Ophthalmology*. 1988;95(5):601–606.
42. Tornambe PE, Hilton GF. Pneumatic retinopexy. A multicenter randomized controlled clinical trial comparing pneumatic retinopexy with scleral buckling. The Retinal Detachment Study Group. *Ophthalmology*. 1989;96(6):772–783. discussion 784.