## Overview

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Trial | Number of Eyes | Disease | Treatment | Length (years) | Frequency of Visits |
| PRIME | 40 | Treatment-naïve NPDR/PDR without center-involved DME | Aflibercept | 2 | Every 4-8 weeks |
| RECOVERY | 40 | Treatment-naïve NPDR/PDR without center-involved DME | Aflibercept | 2 | Every 4-12 weeks |
| TREX-DME | 56 | DME | Ranibizumab or Ranibizumab with laser | 3 | Every 4-16 weeks |

## RECOVERY acronyms

**DRCR** Network = Diabetic Retinopathy Clinical Research Network

**DRSS** = Diabetic Retinopathy Severity Scale

**IAI** = intravitreal aflibercept injection

**ISI** = ischemic index (RNP area/total visible retina)

**PDR** = proliferative diabetic retinopathy

**PRP** = pan-retinal photocoagulation

**RIDE** and **RISE** = Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Secondary Involvement Secondary to Diabetes Mellitus

**RNP** = retinal nonperfusion

**SD OCT** = spectral domain optical coherence tomography

**VEGF** = vascular endothelial growth factor

## PRIME acronyms

**AE** = adverse event

**CRC** = central reading centers

**CST** = central subfield thickness (similar to CRT, CFT, etc.)

**DME** = diabetic macular edema

**DR** = diabetic retinopathy

**DRSS** = diabetic retinopathy severity scale

**FP** = fundus photography

**IAI** = intravitreal aflibercept injections

**IRMA** = intraretinal microvascular abnormalities

**NEI VFQ** = National Eye Institute Visual Function Questionnaire

**NPDR** = non-proliferative diabetic retinopathy

**NVE** = neovascularization elsewhere

**OCT** = optical coherence tomography

**PDR** = proliferative diabetic retinopathy

**PLI** = panretinal leakage index

**PRIME** = Intravitreal Aflibercept as Indicated by Real-Time Objective Imaging to Achieve Diabetic Retinopathy Improvement

**PRN** = *pro re nata (*as needed)

**SAE** = serious adverse event

**UWFA** = ultra-widefield fluorescein angiography

**VEGF-A** = vascular endothelial growth factor-A

## TREX-DME acronyms

**CRT** = central retinal thickness

**DRCRN** = Diabetic Retinopathy Clinical Research Network

**GILA** = treat and extend with angiography-GuIded macular LAser photocoagulation

**LOESS** = locally weighted regression

**RETAIN** = Efficacy and Safety of Ranibizumab in Two “Treat and Extend” Treatment Algorithms Versus Ranibizumab As Needed in Patients with Macular Edema and Visual Impairment Secondary to Diabetes Mellitus

**TREX** = TReat and EXtend without macular laser photocoagulation

**T/E** = treat and extend

## RECOVERY

**Intravitreal Aflibercept for Retinal Nonperfusion in Proliferative Diabetic Retinopathy**

1 year, prospective, randomized, open-label study

### Purpose

* Evaluate the impact of intravitreal aflibercept (Eylea; Regeneron) on RNP in eyes with PDR without DME
* Designed to investigate change in RNP and prospect of retinal reperfusion, with regular aflibercept treatments and to evaluate for the possibility of dose-dependent response of aflibercept on RNP evolution
* Designed with the anticipation of detecting extensive areas of reperfusion of nonperfused retina using UWF FA following aflibercept therapy

### Design

* Used UWF angiography among patients without DME with PDR and severe RNP at baseline in all eyes
  + RNP was defined as an absence of 4th-order and higher order vessels
  + RNP was assessed during the late venous phase of the angiogram to avoid the possibility of leakage from NV confounding the results
    - Phases of UWFA:
* Early - 45 s
* Middle - 2.5 min
* **Late** - 5 min
* UWF steered peripherally (nasally, temporally, superiorly, and inferiorly)
* Monthly vs. quarterly intravitreal 2 mg aflibercept (n = 20 each)
* Monthly: 28 +/- 7 days
* Quarterly: weeks 0, 12, 24, 36
  + - Quarterly cohort monitored monthly to week 12
    - Treated differently if prespecified criteria met
    - Prespecified criteria:
* Increased NV
* BCVA loss >= 5 letters because of progressive DME or PDR
* Development of DME causing vision loss
* Patients in either cohort could receive rescue PRP treatment if progressive PDR was observed despite 3 monthly aflibercept injections

### 

### Outcome measures

* Primary
  + Total RNP area change (mm2) from baseline to year 1
* Secondary
  + ISI
  + DRSS scores
  + VA
  + CRT
  + Adverse events

### Inclusion criteria

* Patients with PDR with ETDRS BCVA >= 19 letters (Snellen equivalent: 20/400)
* Substantial nonperfusion (>20 disc areas) on UWF FA

### Exclusion criteria

* Prior systemic or intravitreal anti-VEGF treatment
* History of vitreoretinal surgery or PRP
* Clinically relevant DME (required intervention, determined by investigator)
* CRT > 320 um in study eye, determined by SD OCT

### Results

* No statistically significant decrease in total area of RNP from baseline to 1 year
* Aflibercept treatment did seem to have a biological impact on RNP in a dose-dependent fashion
* Mean RNP increased significantly among eyes dosed quarterly
* Continuous VEGF inhibition > intermittent VEGF inhibition with regard to reducing progression of RNP in DR
* RNP outcomes favored monthly dosing
* Many eyes demonstrated increased areas of RNP longitudinally (n = 24, 66.7%)
  + More common in quarterly dosing (n =14, 77.8%)
* Proportion of eyes (n = 12, 33.3%) demonstrated localized areas of apparent reperfusion of nonperfused retina
* More commonly in the monthly cohort (n = 8, 44.4%)
* Reduction of RNP progression with monthly compared to quarterly dosing
* Total patient population results
  + Mean area of RNP increased
  + ISI increased significantly
  + RNP increased significantly within the 15 mm zone
  + Total area of NV decreased dramatically
* Eyes dosed quarterly demonstrated statistically significant progression of RNP in multiple concentric grading zones
* Eyes dosed monthly demonstrated statistically significant progression of RNP only within the largest concentric zone
* Retinal vasculature in the mid periphery may be particularly sensitive to progressive vascular damage

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| --- | --- | --- | --- |
| **TABLE**. Summary of IAI Monthly vs. Quarterly (4 vs. 12 weeks) Results in RECOVERY  From Baseline to Year 1 | | | |
|  | Cohort | |  |
|  | Monthly (n = 20) | Quarterly (n = 20) | *P* Value |
| Mean number of aflibercept injections | 11.0 | 3.95 |  |
| DRSS scores improvement of 2 steps or more (%) | 74 | 67 |  |
| Increase in mean total RNP (mm2) | Stable at 264  (P = 0.70) | 207 to 268  (P = 0.01) | 0.050 |
| Increase in mean total area of RNP (mm2) | 235 to 266 | | 0.180 |
| Increase in ISI (%) | 25.8 to 31.9 | | 0.004 |
| DRSS = Diabetic Retinopathy Severity Scale; IAI = intravitreal aflibercept injection;  ISI = ischemic index; RNP = retinal nonperfusion | | | |

### Discussion

* Progressive RNP expansion continues to occur despite regular anti-VEGF dosing
* May not be applicable to NPDR, concurrent DME, or venous occlusion patients, or those with less extensive RNP
* Small areas of reperfusion is a finding that is more common among monthly dosed patients compared with quarterly dosed patients
* Potential mechanisms of reperfusion is alleviation of a leukostatic plug
  + Plugs can be dissolved by anti-VEGFs and restore vascular flow
* Only statistically significant prognostic biomarker identified for progression to a PDR event was the presence of baseline RNP within the posterior pole

### Conclusions

* No identified widespread retinal reperfusion but certain zones were identified in some patients
* Dose-dependent response with a reduction of RNP progression with monthly compared to quarterly aflibercept dosing

### Notes

* DR leads to vision loss through DME and PDR
* VEGF is a key driver of DR
* Anti-VEGFs
  + Ranibizumab = Lucentis (Genentech)
  + Aflibercept = Eylea (Regeneron)
  + Bevacizumab = Avastin (Genentech)
* Anti-VEGF injections: slow progression of PDR, improve DRSS levels
* Sham treatment: the doctor goes through the motions without actually performing the treatment
* PDR events reduced in RIDE and RISE
* VEGF blockade can impact RNP progression
* Ischemic index (ISI) = RNP area/total visible retina

## PRIME

**Real-time Photographic- and Fluorescein Angiographic-Guided Management of Diabetic Retinopathy: Randomized PRIME Trial Outcomes**

Prospective, randomized phase 2 trial

### Purpose

* Assess safety and efficacy of PRN IAI in managing DR guided by the real-time DRSS level or PLI assessment among eyes with severe PR or NDPR without DME
* Want to find an optimal approach (DRSS vs. PLI)

### Design

* 40 eyes with DR (NPDR or PDR) received monthly IAIs until DRSS improvement >= 2 steps
* DRSS-guided vs. PLI-guided management strategies
  + DRSS level determined by CFP
    - Graded by a trained image analyst
  + PLI determined by UWFA
    - Automated, quantitative UWFA image analysis platform was used
    - Used early and late images
    - Leakage was defined as increased hyperfluorescence in area or intensity in the late phase compared to the early phase
    - Trained image analysts corrected any leakage segmentation errors and determined the region of interest enclosing total analyzable retinal area for each time point
    - PLI percentages were calculated: area of leakage/area of interest \* 100.
* Treatment Reinitiation
  + DRSS: 1 step worsening of DRSS compared to the best DRSS level achieved
  + PLI: PLI increased to 50% or higher of the difference between baseline and threshold PLI
    - threshold PLI + [(baseline PLI – threshold PLI)/2]
* Monthly visits
  + ETDRS BCVA testing
  + Ophthalmic examination
  + SD-OCT imaging
  + FP
  + UWFA

### Outcome Measures

* Safety
* Changes in DRSS and PLI

### Inclusion criteria

* Type 1 or 2 diabetes
* DRSS level 47A-71A
* ETDRS BCVA >= 20/800

### Exclusion criteria

* Previous systemic or intravitreal anti-VEGF treatment in the study eye within 24 weeks of screening
* Intravitreal or peribulbar corticosteroids in the study eye within 12 weeks of screening
* Any previous treatment with dexamethasone or fluocinolone acetonide in the study eye
* History of vitrectomy in study eye
* History of PRP
* SD-OCT CST > 320 um
* Central DME causing loss of VA
* Current vitreous hemorrhage that obscured determination of DRSS

### Results

* 1 year (52 weeks)
  + 95% improvement in DRSS by >=2 steps
  + 97% of eyes required at least 1 PRN IAI
* NDPR vs. PDR eyes at baseline achieved a DRSS improvement of >= 2 steps after a mean 4.9 and 3.6 IAIs (P = .03)
* 2 eyes developed a PDR event at week 52 following 5 months of quiescence
* Need 2 step DRSS improvement to initiate PRN IAI dosages
  + Most patients required IAI retreatment every 3-4 months and deterioration of PLI preceded DRSS level worsening
* No significant differences were observed at week 52 between arms for any visual or anatomic changes
* Outcomes and treatment burden appeared similar between arms
* Notable differences:
  + Every eye experienced DRSS worsening
  + PLI worsening may precede DRSS worsening
    - Could be used as an early biomarker suggesting impending DR severity worsening
* Recurrence of leakage may precede DR worsening
* Suggest retreatment every 3-4 months
* PLI arm showed decreased PLI compared to baseline and the DRSS arm did not

|  |  |  |  |
| --- | --- | --- | --- |
| **TABLE**. Comparing DRSS- vs. PLI-guided Arms in PRIME  From Baseline to Year 1 | | | |
|  | Cohort | |  |
|  | DRSS-guided (n=20) | PLI-guided (n=20) | *P* Value |
| Mean IAI | 5.6 | 7.1 | 0.035 |
| Patients with DRSS worsening\* | 100% | 59% | 0.010 |
| Mean PLI decrease | -18.2% (P = 0.49) | -54.6% (P <0.0001) |  |
| \*In eyes requiring PRN IAI; DRSS = Diabetic Retinopathy Severity Scale; IAI = intravitreal aflibercept injection; PLI = panretinal leakage index | | | |

### Discussion

* Close clinical follow up is important even among eyes that achieve substantial DRSS improvements with apparently quiescent disease
* Limitations
  + High rate of LTFU
  + Modification of pure DRSS grading when specific structural lesions (venous beading and IRMA) did not change after 2 consecutive treatments
  + Lack of consistent DRSS and PLI grading for clinic

### Notes

* Retreatment protocols

1. Fixed interval
2. PRN
3. Treat-and-extend

* 2 and 3 are based presence, absence, or change in fluid visualized by OCT for nAMD and DME
* DRSS based on CFP, guides clinical management of DR
* DRSS impractical for clinical practice because of the strict grading methodology, and ability of investigators to determine DRSS score is limited
* Structural lesions: venous beading and IRMA

## ETDRS Report Number 12, 1991

Fundus Photographic Risk Factors for Progression of Diabetic Retinopathy

* ETDRS - Early Treatment Diabetic Retinopathy Study
* Randomized clinical trial
  + Aspirin (650 mg once daily) or a placebo
  + Photocoagulation: early vs. deferred
  + Observe natural course of DR in initially untreated eye
  + 3711 diabetic patients with DR
  + Each eye had to meet either of the following definitions:
    - Moderate or severe NPDR or early PDR, absence of macular edema, VA of 20/40 or better
    - Any degree of NPDR (including MAs only) or early PDR, prescence of ME, and VA of 20/200 or better
* Sponsored by National Eye Institute
* DRS - Diabetic Retinopathy Study
  + Definition for severe stage of NPDR
  + Abnormalities
    - Hemorrhages and/or MAs
    - Cotton-wool spots (soft exudates)
    - Intraretinal microvascular abnormalities (IRMAs)
* Important factors in predicting progression
  + Intraretinal microvascular abnormalities (IRMAs)
  + Hemorrhages
  + Microaneurysms
  + Venous beading
* DRSS - Diabetic Retinopathy Severity Scale
  + Divides DR into 13 levels
  + Ranges from absence of DR to severe vitreous hemorrhage
  + Describes overall retinopathy severity and change in severity over time
  + Orderly progression of risk with increasing category
  + Worsening of two or more levels measures retinopathy severity
  + <= 53 NPDR
  + >= 61 PDR

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## TREX DME Year 1

**Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for DME**

Phase I/II, multicenter, prospective, randomized, controlled clinical trial

* Palmetto Retina Center (West Columbia, SC)
* Retina Consultants of Houston (Houston, TX)
* Retina-Vitreous Associates Medical Group (Los Angeles, CA)

### Purpose

* Compare monthly dosing with a treat and extend algorithm using ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation for center-involving DME

### Design

* 150 eyes from 116 subjects
* 3 cohorts (1:2:2)
  + Monthly (n = 30)
    - 0.05 ml IVT injections of ranibizumab 0.3 mg every 4 weeks
  + TREX (n = 60)
    - TREX = TReat and EXtend without macular laser photocoagulation
    - 4 monthly injections of ranibizumab 0.3 mg followed by a treat and extend (T/E) algorithm based on disease activity (at week 12, eyes with CRT <= 325 um → T/E)
    - Eyes with CRT > 325 um at week 12 continued monthly treatments until CRT achieved was 325 um or less
  + GILA (n = 60)
    - GILA = treat and extend with angiography-GuIded macular LAser photocoagulation
    - 4 monthly injections of ranibizumab 0.3 mg followed by T/E algorithm based on disease activity (at week 12, eyes with CRT <= 325 um → T/E)
    - Received angiography-guided macular laser photocoagulation at month 1 and again every 3 months for microaneurysm leakage (present on FA)
      * Spot size was maintained at 100 µm in all eyes
      * Laser power and duration were left to the investigator’s discretion
* If both eyes of a subject were enrolled, the eyes were randomized to different treatment groups
* When the study eye entered the T/E phase, the baseline CRT was recorded and used for treatment interval determination from that point forward
  + The treatment interval at each visit was extended by 2 weeks, maintained, or decreased by 2 weeks according to the CRT visit at that visit compared with baseline
* Visits
  + ETDRS BCVA testing at 4 m
  + Slit-lamp and dilated ophthalmic examination
  + SD OCT
* T/E algorithm
  + Treatment interval was extended by 2 weeks, maintained, or decreased by 2 weeks according to the CRT at that visit compared with baseline
  + New baseline CRT was established if the retinal thickness had improved by 20% from baseline for 3 consecutive visits with <50 um variability
* Primary outcome measure
  + Change in mean ETDRS BCVA from baseline
* Secondary outcome measures
  + Mean change in CRT
  + Total number of IVT injections
  + Percentage of patients gaining or losing 10 or 15 ETDRS letters at month 12
  + Incidence and severity of ocular and nonocular adverse events

### Inclusion criteria

* Subjects with DM and center-involving DME
* BCVA 79-24 letters (20/25 -20/320 Snellen equivalent)

### Exclusion criteria

* Prior IVT injections of anti-VEGF medications or corticosteroids within the previous 12 weeks
* Prior focal macular laser photocoagulation treatment

### Results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **TABLE**. TREX-DME 1 Year Outcomes | | | | |
|  | Cohort | | |  |
|  | Monthly | TREX | GILA | *P* value |
| 12 week BCVA improvement (letters) | 4.2 | 7.7 | 5.6 | - |
| 1 year BCVA improvement (letters) | 8.6 | 9.6 | 9.5 | 0.80 |
| Change in CRT (µm) | -123 | -146 | -166 | 0.47 |
| Mean number of laser treatments per pt | - | - | 3.1 | - |
| Mean number of injections | 13.1 | 10.7\* | 10.1\* | < 0.001 |
| 1 year >= 10 ETDRS letters improvement | 12 (41%) | 21 (40%) | 25 (45%) | - |
| 1 year >= 15 ETDRS letters improvement | 7 (24%) | 14 (27%) | 18 (32%) | - |

* 137 eyes (91%) completed the 1-year end point visit
* No significant differences between the cohorts in the percentage gaining/losing 2 and 3 lines of vision
* No cases of endophthalmitis
* Total incidence of Anti-Platelet Trialsists’ Collaboration events: 4.7%
* No eyes in the Monthly and GILA cohorts and only 1 eye in the TREX cohort lost >=10 letters at 1 year
* 175 angiography-guided laser treatments were performed in the GILA cohort during the 1st year of treatment

|  |  |
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| **TABLE**. GILA Treatments in the 1st Year | |
| Mean number of laser spots per treatment | 54 (range, 5-254 spots) |
| Mean power used | 77 mW (range, 50-143 mW) |
| Mean laser duration | 94 ms (range, 35-110 ms) |

### Conclusions

* TREX significantly decreases the number of injections given while providing similar visual and anatomic outcomes compared with monthly dosing at 1 year
* Adding GILA did not significantly improve outcomes at 1 year

### Limitations

* No centralized reading center for CRT measurement
* Not powered sufficiently to detect small differences between cohorts
* T/E algorithm may have been too conservative
* Both eyes were able to be enrolled, so there is a potential for bilateral effects from IVT ranibizumab
* May not be applicable to other T/E algorithms

### Notes

* T/E dosing of anti-VEGF medications has been studied and is commonly used for nAMD, not studied rigorously for DME
* Most robust visual outcomes have been achieved with consistent monthly dosing
* Less frequent dosing has been shown to effectively reduce retinal thickness and improve vision
* T/E dosing allows for incremental increases in treatment intervals with the aim of identifying the longest possible interval without disease recurrence
* NAVILAS laser system - navigated laser photocoagulator
  + Provides accuracy and better VA gains compared with conventional focal laser therapy
* Main benefit of T/E strategy is that patients do not have to be seen and treated every month once the disease has been stabilized
* Threshold for treatment extension: 325 um
  + Considered near normal
  + Not so low to prevent subjects with mild residual central fluid from being able to extend treatment
* Some studies have shown that normal CRT is ~270-290 um
* Results of this study are similar to those of the RETAIN trial

## TREX DME Year 2

**Randomized Trial of Treat and Extend Ranibizumab With and Without Navigated Laser Versus Monthly Dosing for DME**

Phase I/II, multicenter, prospective, randomized, controlled clinical trial

* Palmetto Retina Center (West Columbia, SC)
* Retina Consultants of Houston (Houston, TX)
* Retina-Vitreous Associates Medical Group (Los Angeles, CA)

### Purpose

* Prospectively evaluate a T/E algorithm of ranibizumab with and without navigated laser to monthly dosing for center-involving DME

### Methods

* Same methods as year 1
* Primary outcomes
  + Mean change in BCVA from baseline
* Secondary outcomes
  + Mean change in CRT
  + Total number of IVT injections
  + Percentage of patients gaining or losing 10 or 15 ETDRS letters at month 24
  + Incidence and severity of ocular and nonocular adverse events

### Results

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| --- | --- | --- | --- | --- |
| **TABLE**. TREX-DME 2 Year Outcomes | | | | |
|  | Cohort | | |  |
|  | Monthly | TREX | GILA | *P* value |
| 2 year BCVA improvement (letters) | 7.5 | 9.6 | 9.0 | 0.75 |
| Change in CRT (µm) | -139 | -140 | -175 | 0.09 |
| Mean number of laser treatments per pt | - | - | 1.9 | - |
| Mean number of injections in year 2 | 11.6 | 8.2\* | 7.4\* | < 0.001 |
| Number of injections in 24 months | 24.7 | 18.9\* | 17.5\* | < 0.001 |
| Mean treatment interval | 4.3 | 6.2\* | 6.7\* | < 0.001 |
| Mean maximal interval | - | 10.1 weeks | 11.1 weeks |  |

* 136 eyes (91%) completed 1-year endpoint visits
* 119 eyes (79%) completed 2-year endpoint visits
* BCVA gains achieved at month 12 remained stable through the 2nd year
* VA gains were similar and there was no difference between the cohorts when multiple imputations were performed to include eyes that did not reach the 2-year endpoint visit
* Between the TREX and GILA cohorts, there was no significant difference in:
  + Mean treatment interval
  + Mean maximal treatment interval
  + Percentage of eyes extended to 12 weeks
* Total 2-year incidence of Anti-Platelet Trialists’ Collaboration events was 6.7%
* 175 angiography-guided laser treatments were performed in the GILA cohort during the 1st year of treatment, 117 in the 2nd year

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| --- | --- | --- | --- |
| **TABLE**. TREX-DME 2 Year Visual Acuity Outcomes | | | |
|  | Cohort | | |
|  | Monthly | TREX | GILA |
| Eyes that gained 1 line of vision | 13 (52%) | 28 (64%) | 32 (64%) |
| Eyes that gained 2 lines of vision | 12 (48%) | 19 (43%) | 22 (44%) |
| Eyes that gained 3 lines of vision | 6 (24%) | 12 (27%) | 15 (30%) |
| Eyes that lost 1 line of vision | 5 (20%) | 1 (2%) | 3 (6%) |
| Eyes that lost 2 lines of vision | 2 (8%) | 1 (2%) | 0 (0%) |
| Eyes that lost 3 lines of vision | 0 (0%) | 0 (0%) | 0 (0%) |

|  |  |
| --- | --- |
| **TABLE**. GILA Treatments in the 2nd Year | |
| Mean number of laser spots per treatment | 44 (range, 5-254 spots) |
| Mean power used | 77 mW (range, 50-250 mW) |
| Mean laser duration | 93 ms (range, 20-110 ms) |

### Conclusion

* T/E algorithm of ranibizumab in the TREX-DME trial resulted in significantly fewer injections and yielded visual and anatomic gains comparable to monthly dosing at 2 years
* Addition of navigated laser to treat and extend regimen of ranibizumab did not significantly improve visual or anatomic outcomes or significantly reduce treatment burden of IVT injections

### Notes

* Monthly dosing has shown to be effective at reducing retinal thickness and improving vision
* Goal of T/E is to titrate the anti-VEGF dosing based on an individual’s clinical response
* T/E vs. PRN
  + Advantages of T/E
    - Fewer disease recurrences
    - Better long-term visual outcomes and disease stability
    - Fewer patient visits and lower costs
    - More predictable injection workload
  + Disadvantages of T/E
    - Possibility for overtreatment
    - Inability to identify patient who may remain stable without treatment
    - Limited study
* T/E dosing reduced the number of ranibizumab injections from 25 to 18 over 2 years
* Number of injections over 2 years is high compared with the DRCRN Protocol T study (it was 12 for the ranibizumab cohort)
* Mechanisms of action for focal laser photocoagulation are incompletely understood, it has been theorized that decreased edema may result from direct closure of leaking microaneurysms
* Hypotheses of photocoagulation
  + Decreases edema by reducing retinal tissue, leading to decreased retinal blood flow through alterations in autoregulation
  + Reduced retinal blood flow and edema is a result of improved oxygenation after laser treatment
* DRCRN Protocol I (5 years)
  + Eyes receiving focal laser treatment required statistically significantly fewer IVT injections to achieve similar outcomes as those not receiving focal laser treatment for center-involved DME with vision impairment

## TREX DME Year 3

**Long-term outcomes of treat-and-extend ranibizumab with and without navigated laser for DME: TREX-DME 3-year results**

### Purpose

* Evaluate the long-term outcomes of subjects in the TREX-DME trial and assess the sustained effect of treat and extended dosing with and without navigated focal laser therapy for DME

### Methods

* All eyes were examined every 4 weeks and treated PRN with ranibizumab for:
  + > 5 letters vision loss or
  + if the CRT was > 325 µm or
  + if there was > 5 letters vision loss compared with the vision at week 104 visit
* All eyes were eligible to receive focal laser
* All eyes were evaluated at weeks 116, 128, 140, and 152 and were given angiography-guided focal laser therapy if the eye had received >= 2 IVT injections over the previous 90 days
* Primary outcome measures
  + Change in mean BCVA from screening and week 104 to week 156
* Secondary outcomes measures
  + Mean change in CRT
  + Total number of IVT injections and laser treatments
  + Percentage of patients gaining or losing 2 and 3 lines of vision
  + Incidence of severity of ocular and non-ocular adverse events from week 104 to week 156

### Results

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| --- | --- | --- | --- | --- |
| **TABLE**. TREX-DME 3 Year Outcomes | | | | |
|  | Cohort | | |  |
|  | Monthly | TREX | GILA | *P* value |
| 3 year BCVA improvement (letters) | 6.9 | 9.7 | 9.5 | 0.60 |
| Change in CRT (µm) | -129 | -138 | -165 | 0.39 |
| Median number of laser treatments per pt | 1.5 | 1.5 | 1.0 | - |
| Mean number of injections in year 3 | 3.0 | 3.1 | 2.4 | 0.56 |

* 109 eyes (73%) completed the 3-year endpoint
* 19 subjects (26 eyes) were lost to follow-up and 4 subjects (5 eyes) withdrew consent
* 8 subjects (10 eyes) died prior to reaching the 3-year endpoint
* 364 injections were given in the third year
* 86 eyes (79%) required at least 1 ranibizumab injection in the third year

|  |  |  |  |
| --- | --- | --- | --- |
| **TABLE**. TREX-DME 3 Year Visual Acuity Outcomes | | | |
|  | Cohort | | |
|  | Monthly | TREX | GILA |
| Eyes that gained 1 line of vision | 13 (52%) | 28 (64%) | 32 (64%) |
| Eyes that gained 2 lines of vision | 12 (48%) | 19 (43%) | 22 (44%) |
| Eyes that gained 3 lines of vision | 6 (24%) | 12 (27%) | 15 (30%) |
| Eyes that lost 1 line of vision | 5 (20%) | 1 (2%) | 3 (6%) |
| Eyes that lost 2 lines of vision | 2 (8%) | 1 (2%) | 0 (0%) |
| Eyes that lost 3 lines of vision | 0 (0%) | 0 (0%) | 0 (0%) |

### Conclusion

* The improvements achieved after 2 years of treat-and-extend ranibizumab for DME were maintained in the 3rd year