## 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 |
| TREX-DME | 150\* | Center-involved DME | Ranibizumab or Ranibizumab with laser | 3 | Every 4-16 weeks |

\*only 56 of these eyes are included in the OLIVES dataset

*These summaries serve to outline the PRIME and TREX-DME clinical trials. Please refer to the published manuscripts for more information.*

## PRIME acronyms

**BCVA** = best-corrected visual acuity

**CFP** = color fundus photography

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

**DME** = diabetic macular edema

**DR** = diabetic retinopathy

**DRSS** = diabetic retinopathy severity scale

**ETDRS** = Early Treatment Diabetic Retinopathy Study

**FP** = fundus photography

**IAI** = intravitreal aflibercept injections

**NPDR** = non-proliferative diabetic retinopathy

**SD-OCT** = spectral-domain 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)

**PRP** = panretinal photocoagulation

**UWFA** = ultra-widefield fluorescein angiography

**VA** = visual acuity

**VEGF** = vascular endothelial growth factor

## TREX-DME acronyms

**BCVA** = best-corrected visual acuity

**CRT** = central retinal thickness

**DM** = diabetes mellitus

**DME** = diabetic macular edema

**DRCRN** = Diabetic Retinopathy Clinical Research Network

**ETDRS** = Early Treatment Diabetic Retinopathy Study

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

**IVT** = intravitreal injection

**LOESS** = locally weighted regression

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

**T/E** = treat and extend

**VA** = visual acuity

**VEGF** = vascular endothelial growth factor

## PRIME

**Real-time Photographic- and Fluorescein Angiographic-Guided Management of Diabetic Retinopathy: Randomized PRIME Trial Outcomes**1

**Real-Time Diabetic Retinopathy Severity Score Level versus Ultra-Widefield Leakage Index-Guided Management of Diabetic Retinopathy: Two-Year Outcomes from the Randomized PRIME Trial**2

Prospective, randomized phase 2 trial

### Purpose

* Assess safety and efficacy of PRN IAI in eyes with PDR or NDPR without DME
* Compare two approaches for managing DR in real-time: DRSS vs. PLI-guided approach

### Design

* 40 eyes with DR received monthly IAIs until an improvement of ≥ 2 steps on the DRSS was met
* DRSS-guided vs. PLI-guided management strategies
  + DRSS level determined by CFP
    - Graded by a trained image analyst
    - DRSS grading scale was created in 1991, and the scale can be found in Table 11 of ETDRS Report Number 123
      * <= 53 NPDR
      * >= 61 PDR
  + PLI determined by UWFA
    - Used early and late images
    - Leakage areas were composed of regions with increased hyperfluorescence in the late phase compared to the early phase
    - Trained image analysts corrected any leakage segmentation errors and calculated areas of leakage and areas of interest
    - PLI percentages were calculated
      * PLI % = (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]
* At monthly visits, patients underwent:
  + ETDRS BCVA testing
  + Ophthalmic examination
  + SD-OCT imaging
  + FP imaging
  + UWFA imaging

### 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 treatment in the study eye:
  + anti-VEGF pharmacotherapies within 24 weeks of screening
  + corticosteroids within 12 weeks of screening
  + dexamethasone
  + fluocinolone acetonide
* History of vitrectomy or PRP
* SD-OCT CST > 320 µm
* Central DME causing vision loss
* Current vitreous hemorrhage

### Year 1 Results

* 1 year (52 weeks)
  + 95% improvement in DRSS by ≥ 2 steps
  + 97% of eyes required ≥ 1 PRN IAI
* Need 2-step DRSS improvement to initiate PRN IAI dosages
  + DRSS worsening was preceded by PLI worsening in most patients
    - Recurrence of leakage could serve as an early biomarker for DR worsening
  + IAI retreatment every 3-4 months was common
    - Could suggest this in clinical practice
* No significant differences between arms for any anatomic or visual changes
* Outcomes and treatment burden were similar between arms
* PLI arm showed decreased PLI compared to baseline, and the DRSS arm did not
* DRSS-guided vs. PLI-guided outcomes
  + DRSS-guided
    - Mean IAI = 5.6
    - Patients with DRSS worsening in eyes requiring PRN IAI = 100%
    - Mean PLI decrease = -18.2% (P = 0.49)
  + PLI-guided
    - Mean IAI = 7.1
    - Patients with DRSS worsening in eyes requiring PRN IAI = 59%
    - Mean PLI decrease = -54.6% (P <0.0001)
* NPDR vs. PDR outcomes – Year 1
  + NPDR
    - DRSS improvement of ≥ 2 steps Mean IAI = 4.9
  + PDR
    - DRSS improvement of ≥ 2 steps Mean IAI = 3.6

### Year 2 Results

* DRSS-guided vs PLI-guided outcomes
  + DRSS-guided
    - Mean IAI = 3.3
    - Mean PLI decrease = -11% (P = 0.73)
  + PLI-guided
    - Mean IAI = 2.9
    - Mean PLI decrease = -23.6% (P = 0.25)

### Discussion

* Close clinical follow up is important even in eyes that appear quiescent
* Limitations
  + High LTFU rate
  + Modification of pure DRSS grading used in this study
  + DRSS and PLI grading would be difficult to implement into routine clinical care

### Notes

* Types of retreatment protocols

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

* PRN and treat-and-extend protocols are often based on fluid changes visualized by OCT
* DRSS could be impractical for clinical practice because of the strict grading methodology

## TREX DME

Year 1 – **Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for DME**4

Year 2 – **Randomized Trial of Treat and Extend Ranibizumab With and Without Navigated Laser Versus Monthly Dosing for Diabetic Macular Edema: TREX-DME 2-Year Outcomes**5

Year 3 – **Long-Term Outcomes of Treat-And-Extend Ranibizumab With and Without Navigated Laser for Diabetic Macular Oedema: TREX-DME 3-Year Results**6

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 three dosing approaches using ranibizumab 0.3 mg for eyes with center-involving DME:
  + Monthly dosing
  + Treat and extend algorithm with angiography-guided macular laser photocoagulation
  + Treat and extend algorithm without angiography-guided macular laser photocoagulation

### Design

* 150 eyes from 116 subjects
* 3 cohorts – eyes were randomized in a 1:2:2 ratio
  + 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
    - Eyes with CRT > 325 µm at week 12 continued monthly treatments until CRT ≤ 325 µm
  + 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
    - Eyes with CRT > 325 µm at week 12 continued monthly treatments until CRT ≤ 325 µm
    - Received laser at month 1 and again every 3 months for microaneurysm leakage (present on FA)
* If both eyes of a subject were enrolled, the eyes were randomized to different treatment groups
* At visits, patients underwent:
  + ETDRS BCVA testing
  + Slit-lamp and dilated ophthalmic examination
  + SD-OCT imaging
* T/E algorithm
  + Baseline CRT recorded
  + Treatment interval was extended or decreased by 2 weeks or maintained according to CRT compared to baseline
    - Change in CRT within ±10% of baseline CRT – extend by 2 weeks
    - Change in CRT within ±20% of baseline CRT – maintain interval
    - Change in CRT >20% of baseline CRT – decrease interval by 2 weeks
    - Change in CRT <20% of baseline CRT – new baseline if maintained for 3 consecutive visits with ≤ 50 µm 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 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 12 weeks
* Prior focal macular laser photocoagulation

### Year 1 Results

* 137 eyes (91%) completed the 1-year visit
* No significant differences between the cohorts in the percentage gaining/losing 2 and 3 lines of vision
* No cases of endophthalmitis
* No eyes in the Monthly and GILA cohorts and only 1 eye in the TREX cohort lost ≥ 10 letters at 1 year
* 175 laser treatments were performed in the GILA cohort in the 1st year

### Year 2 Results

* 136 eyes (91%) completed the 1-year visit
* 119 eyes (79%) completed the 2-year visit
* BCVA gains achieved at month 12 remained stable through the 2nd year
* 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
* 175 laser treatments were performed in the GILA cohort in the 1st year, 117 in the 2nd year
* T/E dosing reduced the number of ranibizumab injections from 25 to 18 over 2 years

### Year 3 Methods

* All eyes were examined every 4 weeks and treated PRN with ranibizumab for:
  + > 5 letters vision loss or
  + CRT was > 325 µm or
  + > 5 letters vision loss compared with the vision at week 104 visit
* All eyes were:
  + Eligible to receive focal laser
  + Evaluated at weeks 116, 128, 140, and 152
  + Treated with laser therapy if the eye had received ≥ 2 IVT injections in 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 and severity of adverse events from week 104 to week 156

### Year 3 Results

* 109 eyes (73%) completed the 3-year endpoint
* 19 subjects (26 eyes) were lost to follow-up
* 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

### Conclusions

* TREX dosing significantly decreased the number of injections given compared to monthly dosing at 1 year
  + Provides similar visual and anatomic outcomes
* Adding laser treatment did not significantly improve outcomes at 1 year
* Conclusions from the 1st year held true for the 2nd year of the study
* The improvements achieved after the 2nd year of the study were maintained in the 3rd year

### Limitations

* No centralized reading center for CRT measurement
* 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

### Notes

* Consistent monthly dosing has been shown to have the most robust visual outcomes
* Less frequent dosing has been shown to reduce retinal thickness and improve vision
* Main benefit of T/E strategy: lessens treatment burden for patients
* T/E is a form of personalizing anti-VEGF dosing based on an individual’s clinical response
* T/E vs. PRN dosing
  + Advantages of T/E
    - Fewer disease recurrences
    - Better long-term visual outcomes and disease stability
    - Fewer patient visits
    - Lower costs
    - More predictable injection workload
  + Disadvantages of T/E
    - Possibility for overtreatment
    - Inability to identify patient who may remain stable without treatment
* Threshold for treatment extension in this study: 325 µm
  + Considered near normal
* Some studies have shown that normal CRT is ~270-290 µm

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