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Diabetic Retinopathy 3 Symposium

Efficacy, Safety, and Immunogenicity of MYL-1701P Compared With Eylea in Participants With Diabetic Macular Edema: Multicenter Double-Masked Randomized Phase 3 Study

- Susan Bressler, MD, FASRS
- Rajendra Apte, MD, PhD
- Abhijit Barve, MD, PhD, MBA
- Katrin Beckmann, M Sc
- Sunil Patel, MD, PhD
- Daniel Alfaro, MD
- Jan Ernest, MD, PhD
- Rozsa Degi, MD, PhD
- Motohiro Kamei, MD, PhD
- Vishali Gupta, MS
- Annalakshmi Jagatheesan, MD
- Prasanna Ganapathi, MD

Objective:
Compare efficacy and safety of MYL-1701P, a proposed aflibercept biosimilar, with the reference product Eylea® (aflibercept), in participants with diabetic macular edema (DME).

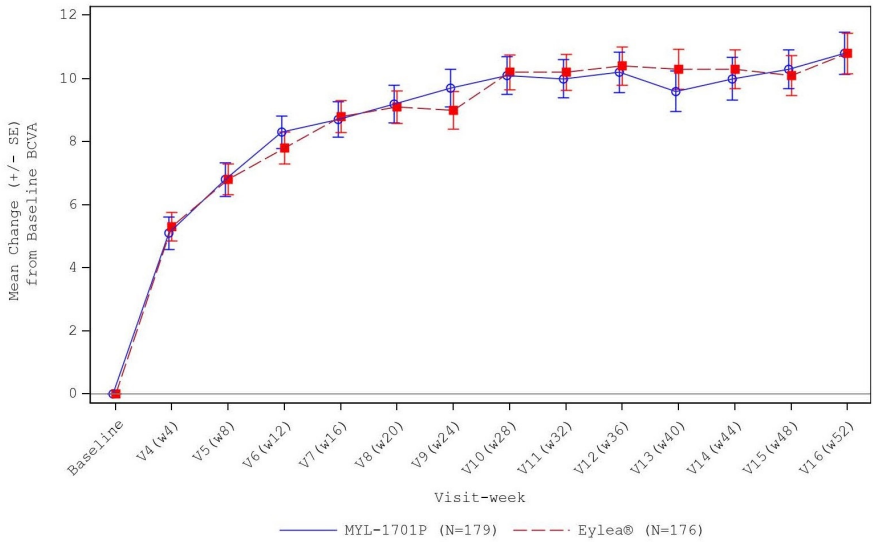
Purpose:
Biosimilars as alternative to biological products potentially increase access and lower health care costs in the management of select retinal diseases. The efficacy, safety and immunogenicity of MYL-1701P was compared with reference aflibercept over 52 weeks.

Methods:
This multi-center, randomized, double-masked, clinical trial dosed eyes with central DME and ETDRS letter score 73 to 38 (~Snellen equivalent 20/40 to 20/200) using 0.5 mg vial formulations of MYL-1701P or reference aflibercept q4w for 5 consecutive intravitreal injections (loading) followed by q8w (maintenance) through week 48. Q4w dosing was permitted in the maintenance phase if pre-specified BCVA or CRT criteria were met. Primary end point was mean change from baseline in BCVA letter score at week 8. Secondary endpoints included change in CRT, BCVA, and number of injections over 52 weeks, incidence of adverse events (AE) and anti-drug antibodies (ADA).

Results:
355 participants with central DME were randomized; 179 to MYL-1701P, 176 to reference aflibercept. At baseline, the mean BCVA and CRT were 62.7 vs. 63.9 letters and 467.9 µm vs. 468.0 µm for MYL-1701P and reference aflibercept, respectively. The week 8 and week 52 visits were completed by 97.2% and 89.9% of the total cohort, respectively. At week 8, the mean change in BCVA was 6.60 vs. 6.56 letters in MYL-1701P vs. reference aflibercept. The adjusted mean difference (90%CI) of 0.04 letters (-1.16, 1.24) (Figure 1) met the primary outcome as the equivalence margin was ±3 letters. At week 52, the mean change in BCVA was 10.76 vs.10.52 letters in MYL-1701P vs. reference aflibercept (adjusted mean difference [90%CI]: 0.24 letters [-1.13, 1.62]). At week 8, the mean change in CRT was -112.15 µm vs. -123.61 µm in MYL-1701P vs. reference aflibercept (adjusted mean difference [90%CI]: 11.46 µm [-3.36, 26.29]) and this remained comparable between groups over time (Figure 2). The proportion of eyes gaining and losing pre-specified number of letters from baseline at week 52 was similar between treatment groups. The incidence of AEs in the MYL-1701P and reference aflibercept groups respectively were as follows: ocular (30.9% vs. 29.5%), serious ocular (0.6% vs. 1.1%), non-ocular (65.2% vs. 65.3%) and serious non-ocular (16.9% vs. 12.5%). No new safety concerns were identified. The mean (SD) total number of injections was 8.4 (2.06) vs. 8.7 (1.76) in MYL-1701P vs. reference aflibercept over 52 weeks. The incidence of treatment induced or treatment boosted ADA was 2.8% vs. 5.7% in MYL 1701P vs. reference aflibercept.

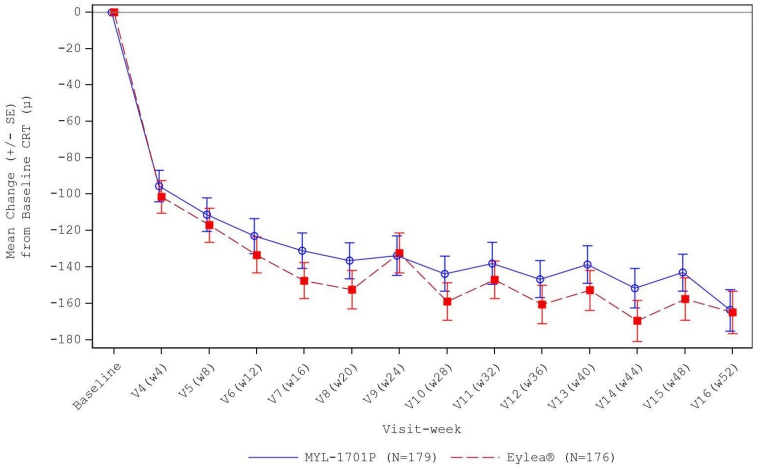
Conclusion:
Therapeutic equivalence confirmed between MYL-1701P and reference product Eylea® based on primary and secondary efficacy analyses, and similar safety and immunogenicity profiles supports the potential use of MYL-1701P as a biosimilar to Eylea.

IRB APPROVAL Yes



BCVA, best-corrected visual acuity; SE, standard error

Figure 1: Mean Change in BCVA (letters) from Baseline: INSIGHT Study



CRT, central retinal thickness; SE, standard error

Figure 2: Mean Change in CRT (µm) from Baseline in DME: INSIGHT Study

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Diabetic Retinopathy 3 Symposium

0.19 mg Fluocinolone Acetonide Implant Leads to Superior Vision, Anatomical, and Treatment Burden Outcomes in Eyes With Better Baseline Visual Acuity (≤20/40)

- Victor Gonzalez, MD

Objective:
To report the long-term safety and functional outcomes of eyes divided by their baseline vision, ≥20/40 or <20/40, following treatment with the 0.19 mg fluocinolone acetonide (FAc) implant for center involving diabetic macular edema (CI-DME) in the PALADIN study.

Purpose:
The USER study highlighted the visual and reduced treatment burden benefit of treating eyes with good baseline visual acuity, 20/40 or better (≥20/40). This report provides real world evidence from the 3-year prospective, phase IV PALADIN study that treating better seeing eyes with the 0.19 mg FAc implant leads to superior visual and treatment burden benefit.

Methods:
202 eyes from 159 patients with CI-DME were enrolled in the PALADIN study and treated for up to 36 months with the 0.19 mg FAc implant. Study assessments were taken at baseline, day 7, month 2, month 3, and then every 3 months up to 36 months. This report focuses on vision- and treatment burden-related outcomes on a subset of eyes divided by baseline visual acuity, ≥20/40 (n=65) and <20/40 (n=126).

Results:
Post-FAc, eyes with a baseline BCVA of ≥20/40 (mean 77.5 letters) maintained their vision through month 36 (mean 75.52 letters) with a mean change from baseline of -2.0 letters (p=0.459). Furthermore, eyes with a baseline BCVA of <20/40 (mean 53.1 letters) significantly improved their vision through month 36 (mean 61.3 letters) with a mean change from baseline of +8.2 letters (p=0.005). In the 36 months pre-FAc, 70.2% and 65.1% of the ≥20/40 and <20/40 eyes were receiving ≥3 yearly treatments, respectively. Conversely, post-FAc 73.1% and 63.5% of the ≥20/40 and <20/40 eyes were receiving ≤2 adjunctive yearly treatments, respectively. Additionally, both the ≥20/40 and<20/40 had significant reductions in the recurrence of edema, as measured by retinal thickness amplitude and standard deviation, when comparing pre- versus post-FAc. Finally, the ≥20/40 subgroup had a lower incidence of intraocular pressure (IOP) related events, such as IOP elevation >30 mmHg and incisional IOP lowering surgery.

Conclusion:
Real world data from the 3-year prospective, phase IV PALADIN study highlights that vision was maintained or improved regardless of baseline visual acuity, and no new safety concerns were identified. PALADIN real world data provides supportive evidence that better seeing eyes at baseline (≥20/40), compared to worse seeing eyes (<20/40), have superior vision, anatomy, and reduced treatment burden when treated with the 0.19 mg FAc implant.

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Diabetic Retinopathy 3 Symposium

Factors Associated With Fluctuations in Central Subfield Thickness in Patients With Diabetic Macular Edema Using 2 Clinical Trial Databases

- Matthew Starr, MD
- Mirataollah Salabati, MD
- Louis Cai
- Raziyeh Mahmoudzadeh, MD
- Ajay Kuriyan, MD, MS

Objective:
We aim to identify any baseline characteristics that may predict which patients with diabetic macular edema (DME) may develop fluctuations in central subfield thickness (CST), as previous work has shown CST fluctuations to be associated with worse visual acuity in patients with DME.

Purpose:
To identify baseline metrics that are associated with central subfield thickness (CST) fluctuations in patients with diabetic macular edema (DME) using data from two large clinical trials (DRCR Protocols T and V).This was a post-hoc analysis of clinical trial databases. The standard deviation (SD) of all recorded CSTs for each patient during the study period were used to quantify the fluctuations in CST per patient in each protocol. The CST SD for each patient was then analyzed against baseline metrics to identify any metrics that may be associated with significant changes in the fluctuation of CST. Each protocol was analyzed separately.

Methods:
This was a post-hoc analysis of clinical trial databases. The standard deviation (SD) of all recorded CSTs for each patient during the study period were used to quantify the fluctuations in CST per patient in each protocol. The CST SD for each patient was then analyzed against baseline metrics to identify any metrics that may be associated with significant changes in the fluctuation of CST. Each protocol was analyzed separately.

Results:
A total of 1,197 eyes were included in the analysis. The mean CST SD in Protocol T was 56.4 ± 35.1 microns and in Protocol V it was 36.6 ± 28.4 microns. On multivariate linear regression analysis controlling for patient age, gender, insulin use, baseline Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA), baseline CST, baseline urine albumin, baseline urine albumin/creatinine ratio, and treatment modality for significant CST SD changes, only baseline VA (for every 10 ETDRS letters, -9.52, 95% Confidence Interval (CI) 11.89 to -7.15, $p < 0.0001$), baseline CST (for every 10 microns, 0.87, 95% CI 0.58 to 1.16, $p < 0.0001$), and the baseline urine albumin/creatine ratio (for every 1000 mg/g, 3.50, 95% CI 0.58 to 6.49, $p = 0.0190$) were associated with significant shifts in CST SD in Protocol T. Similarly in Protocol V, only gender (2.18, 95% CI 0.30 to 4.06, $p = 0.0227$), Type 2 diabetes (-7.37, 95% CI -13.64 to -1.11, $p = 0.0209$), baseline CST (2.51, 95% CI 2.21 to 2.82, $p < 0.0001$), systolic blood pressure (for every 1 millimeter of mercury, 0.11, 95% CI 0.01 to 0.21, $p = 0.0261$), observation with deferred anti-vascular endothelial growth factor (VEGF) injections (5.04, 95% CI 2.51 to 7.58, $p < 0.0001$), and prompt anti-VEGF injections (-6.51, 95% CI -9.07 to -3.96, $p < 0.0001$) were significantly associated with fluctuations in CST SD.

Conclusion:
Worse visual acuity at baseline, baseline renal disease, hypertension, male gender, type 2 diabetes, and delayed anti-VEGF treatment may be associated with increased fluctuations in CST in patients with diabetic macular edema. These metrics may aid physicians in predicting which patients are more prone to significant fluctuations in CST.

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Diabetic Retinopathy 3 Symposium

Phase 2 Study of THR-149, a Plasma Kallikrein Inhibitor in Patients With DME Who Respond Suboptimally to Anti-VEGF Treatment (Month 6 Results of Part A of the KALAHARI Study)

- Rahul Khurana, MD, FASRS
- David Warrow, MD
- Joel Pearlman, MD, PhD
- Victor Gonzalez, MD
- David Boyer, MD

Objective:
The objective of Part A of the KALAHARI study presented here was to select the dose of THR-149 to be assessed in Part B in comparison to aflibercept for the treatment of diabetic macular edema (DME) in subjects who respond suboptimally to anti-VEGF therapy.

Purpose:
Plasma kallikrein (pKal) is a VEGF-independent key driver of DME. THR-149 is a selective, potent inhibitor of pKal which may be effective in treating the ~40-50% of patients with DME who respond suboptimally to anti-VEGF treatment.

Methods:
Adult subjects with a diagnosis of DME ≤36 months prior to screening were prospectively recruited. Subjects had to have ≥5 anti-VEGF injections (last injection 3-8 weeks before screening), central subfield thickness (CST) ≥320µm on optical coherence tomography, and best-corrected visual acuity (BCVA) between 73 and 39 ETDRS letters. They were randomized into 3 different dose groups (0.01, 0.04 and 0.13 mg), received 3 monthly injections of THR-149 and were followed until Month (M) 6. Key endpoints included safety and mean changes from Baseline (BL) in BCVA letter score and in CST at M3 and at M6.

Results:
There were 20 subjects randomized into the study per protocol. 80% of the subjects received more than 5 anti-VEGF treatments in the year preceding screening. Demographics and BL characteristics in the study eye were similar across groups. At BL, mean (SD) BCVA and CST were 62.8 (10.67) letters and 449.6 (86.78) µm, respectively. No serious adverse events (AEs) occurred in the study eye and all AEs were mild to moderate in intensity. Increases in AE incidence were not seen with increasing dose nor with number of injections. The greatest efficacy was seen in the high dose group with a mean improvement in BCVA of 6.1 letters (95% confidence limit (CI): -0.4 to +12.6 letters) at M3. The BCVA gain was maintained to M6 with no rescue treatments given to any subjects in this group. CST remained stable in the high dose group up to M6 with a mean change from BL of 13.3 µm (95% CI: -37.1 to 63.6 µm) at M3. At the lower doses, gains in BCVA were marginal and some subjects required rescue treatment.

Conclusion:
Three monthly injections of THR-149 were found to be safe and well tolerated. The highest dose of THR-149 (0.13 mg) has been selected for the Part B of the KALAHARI study which is comparing the safety and efficacy of THR-149 to aflibercept in subjects with DME with suboptimal response to anti-VEGFs. Information collected in Part A was also used to amend the design of Part B of the KALAHARI study which is currently recruiting.

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Diabetic Retinopathy 3 Symposium

HORNBILL: Phase 1/2a Study of Safety and Early Response of BI-X in Patients With Diabetic Retinopathy and Diabetic Macular Ischemia Treated With Panretinal Photocoagulation

- Quan Nguyen, MD, MSc, FARVO, FASRS
- Sobha Sivaprasad, FRCOphth
- Chirag Jhaveri, MD, FASRS
- Harsha Sen, MD
- David Brown, MD
- Raj Maturi, MD
- Abosede Cole
- Andrea Giani
- Liz Pearce, OD PhD

Objective:
Diabetic macular ischemia (DMI) is a vision-threatening eye disease with no treatment; HORNBILL is examining the first potential treatment for patients with DMI: BI-X.

Purpose:
DMI is a complication of diabetic retinopathy (DR) that can lead to irreversible vision loss and has no approved treatment. HORNBILL (NCT04424290) is a two-part non-randomized, open-label Phase I/IIa single rising dose (SRD) and randomized, sham-controlled, single-masked, multiple dosing (MD) study examining the safety and efficacy of the anti-ischemia modulator BI-X in patients with DMI.

Methods:
Eligible subjects have DR and evidence of DMI, defined in the SRD part as any degree of disruption in retinal vascularity within the superficial/deep retinal plexus, and in the MD part as a foveal avascular zone (FAZ) size ≥0.5 mm. The completed SRD part comprised three cohorts (0.5 mg, n=3; 1.0 mg, n=3; 2.5 mg, n=6), with each subject receiving one intravitreal dose of BI-X. The primary endpoint of the SRD part was the number of dose-limiting events. The primary endpoint of the MD part is number of subjects with drug-related adverse events (AEs); further MD endpoints include change from baseline in best-corrected visual acuity (BCVA), FAZ size, and central retinal thickness.

Results:
In the SRD part, there were no dose-limiting or drug-related AEs reported; 5 were ocular (conjunctival hemorrhage, ocular hyperemia, mild post-procedural pain, temporary rise in intraocular pressure, vitreous detachment), of which 3 were procedure related (conjunctival hemorrhage, temporary rise in intraocular pressure and mild post-procedural pain). Although the SRD part was not powered for efficacy, there were preliminary signs of vision improvement in the 1.0 and 2.5 mg groups, with mean BCVA improving by 5.3 and 4.0 letters, respectively. Two subjects have enrolled in the ongoing MD part, receiving the maximum feasible dose of BI-X (2.5 mg).

Conclusion:
BI-X was well tolerated by all subjects in the SRD part, with initial signs of efficacy. The effect of 2.5 mg BI-X on BCVA and FAZ size in patients with DMI is now being examined in the MD part.

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Diabetic Retinopathy 3 Symposium

Association Between DRSS Changes and Visual/ Anatomic Outcomes in Patients With Moderately Severe to Severe NPDR: Post Hoc Analysis of PANORAMA

- Diana Do, MD, FASRS

Objective:
To evaluate the association between changes in diabetic retinopathy severity scale (DRSS) score and visual/anatomic outcomes at Week 52, in eyes treated with intravitreal aflibercept injection (IAI) and Sham in the PANORAMA trial.

Purpose:
In PANORAMA, significantly more eyes with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) treated with IAI achieved a ≥2-step DRSS improvement at 52 weeks vs sham. Understanding the relationship between DRSS changes and visual/anatomic outcomes can inform clinical decision-making regarding the proactive treatment of moderately severe to severe NPDR.

Methods:
This post hoc analysis included patients with moderately severe to severe NPDR who were treated with IAI 2 mg q16 weeks after 3 monthly doses and one q8 interval, IAI 2 mg q8 weeks after 5 monthly doses, or sham through week 52 in PANORAMA. Data for both IAI treatment groups were combined. Changes in BCVA, CST, and leakage and nonperfusion areas from baseline to week 52 were evaluated across the following three subgroups of DRSS response within IAI and sham treatment groups: (a) eyes with worsening or no change on DRSS, (b) eyes with 1-step DRSS improvement, and (c) eyes with ≥2-step DRSS improvement. Corresponding numbers of patients included in each DRSS subgroup were, respectively, 17, 57, and 195 for IAI, and 70, 43, and 20 for sham.

Results:
The proportions of patients with worsening/no DRSS change, 1-step, and ≥2-step DRSS improvement at Week 52 were 6.3%, 21.2%, 72.5% in the IAI group, and 52.6%, 32.3%, 15.0% in the sham group, respectively. The corresponding mean BCVA change from baseline at week 52 was 0.4, 1.3, 1.2 letters with IAI, and –0.7, 0.9, 1.7 letters with sham (difference [95% CI] in BCVA change between the subgroups of eyes with ≥2-step improvement vs worsening/no DRSS change in the sham group was 2.4 [0.1, 4.7] letters). Mean change in CST was –9.7, –19.0, –22.4 µm with IAI and 13.5, 0.2, –5.4 µm with sham (difference [95% CI] in CST change between the subgroups of eyes with ≥2-step improvement vs worsening/no DRSS change in the IAI group was –12.7 [–23.8, –1.6] µm). The corresponding mean change in leakage area from baseline was –7.7, –12.6, and –15.6 mm^2 with IAI, and 0.6, –1.9, and –1.3 mm^2 with sham (difference [95% CI] in leakage area between the subgroups of eyes with ≥2-step improvement vs worsening/no DRSS change in the IAI group was= –7.9 [–11.5, –4.3] mm^2). Mean change in nonperfusion area was 0.08, 0.08, 0.07 mm^2 with IAI, and 0.23, 0.13, 0.14 mm^2 with sham.

Conclusion:
A ≥2-step DRSS improvement at Week 52 was associated with a trend of greater improvements in BCVA, CST, and leakage area, but not nonperfusion area, within both IAI and sham groups.

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Diabetic Retinopathy 3 Symposium
Benefits and Value of Treatment for Diabetic Macular Edema

- Paul Hahn, MD, PhD, FASRS
- Geoffrey Emerson, MD, PhD, FASRS
- Jill Blim, MS
- Philip Ferrone, MD, FASRS
- Karen Mulligan, PhD
- Seth Seabury, PhD

Objective:
What are the economic benefits associated with treatment for diabetic macular edema (DME)?

Purpose:
To simulate economic outcomes for individuals with DME and estimate the economic and societal value of direct and indirect benefits associated with DME treatment.

Methods:
A microsimulation model simulated self-reported vision and economic outcomes for individuals with DME. We incorporated treatment effects for anti-vascular endothelial growth factor (aVEGF), steroids, or laser monotherapy into the microsimulation using DRCR clinical trial data and a model that translated visual acuity (VA) to self-reported vision (SRV). Individuals were simulated under four different treatment arms to generate the direct and indirect benefits: untreated, aVEGF, laser, and steroids. Individual results were scaled up to calculate benefits for a representative United States (US) DME cohort using real-world 2020 treatment utilization data from the Vestrum Health database. Cost scenarios were modeled with the cohort-level benefits from the microsimulation to estimate the net value of treatment.

Results:
In the model, excellent or good SRV roughly corresponded to 20/40 or better VA. A hypothetical 51-year old with DME treated with aVEGF therapy would spend an additional 5.4 years with excellent or good SRV and 4.0 fewer years with fair or poor SRV relative to being untreated. Furthermore, a treated individual would experience 1.4 years in life expectancy gains and 2.1 quality-adjusted life year gains compared with a scenario where they are untreated. Indirect benefits for this individual relative to an untreated one included more years working and greater earnings over their lifetime with fewer years with a disability or making disability claims. Similar benefits were seen with steroid and laser therapy, but aVEGF was associated with greatest benefit. For the estimated US DME cohort of 1.1 million people, assuming real-world 2020 treatment patterns (69% receive aVEGF therapy (including combination treatment), 3% laser monotherapy, 1% steroid monotherapy, and 28% untreated), total benefit 20 years after treatment initiaiton was modeled at $78.5 billion (direct benefit $71.3 billion and indirect benefit $5.1 billion). Depending on the aVEGF injection frequency and assumed durability of treatment, net value (benefit net cost) ranged from $47.3-$63.2 billion by year 20.

Conclusion:
Treatment for DME provides substantial economic benefits to patients and society, both directly through improved vision, life expectancy, and quality of life gains and indirectly through improved employment and disability outcomes.

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