# A Novel Bicyclic Peptide Inhibitor of Plasma Kallikrein, THR-149, for the Treatment of Diabetic Macular Edema (DME): Clinical and Pre-Clinical Evidence

Francesco Bandello[1], Ramin Tadayoni[2], Sunil Patel[3], Pravin Dugel[4,5], Brian Berger[6], Mitchell Fineman[7], Glenn Jaffe[8], Jeffrey Heier[9], Tine Van Bergen[10], Isabelle Etienne[10], Petra Kozma[10], Arshad M. Khanani[11]

[1]Department of Ophthalmology, IRCCS Ospedale San Raffaele, University Vita-Salute, Milan Italy
[2]Department of Ophthalmology, Hôpital Lariboisière (AP-HP), Université Paris, France
[3]Retina Research Institute of Texas, Abilene, TX, USA
[4]Retinal Consultants of Arizona, Phoenix, AZ, USA
[5]Phoenix Eye Institute, Banner University Medical Center, Phoenix, AZ, USA
[6]Retina Research Center, Austin, TX, USA
[7]Mid Atlantic Retina, Retina Service of Wills Eye Hospital, Philadelphia, PA, USA
[8]Department of Ophthalmology, Duke University, Durham, NC, USA
[9]Ophthalmic Consultants of Boston, Boston, MA, USA
[10]Oxurion NV, Leuven, Belgium
[11]Sierra Eye Associates, Reno, NV, USA

# Financial Disclosures

- ALLERGAN
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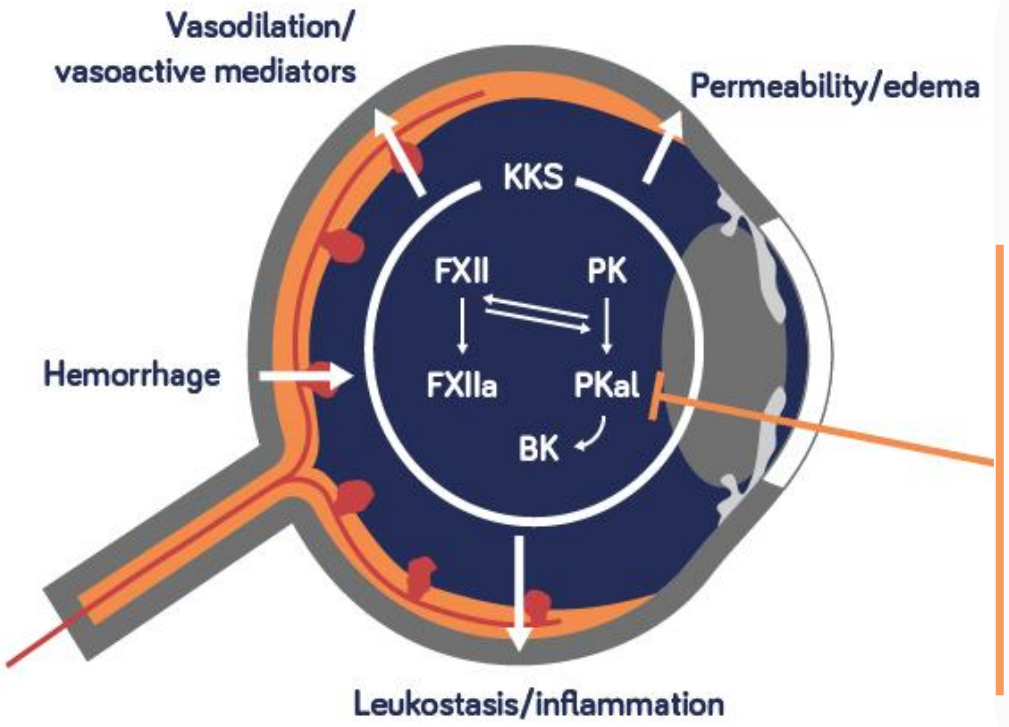
# THR-149 • Highly potent plasma kallikrein inhibitor for DME

## Highly potent, selective and stable peptide targeting a VEGF-independent pathway



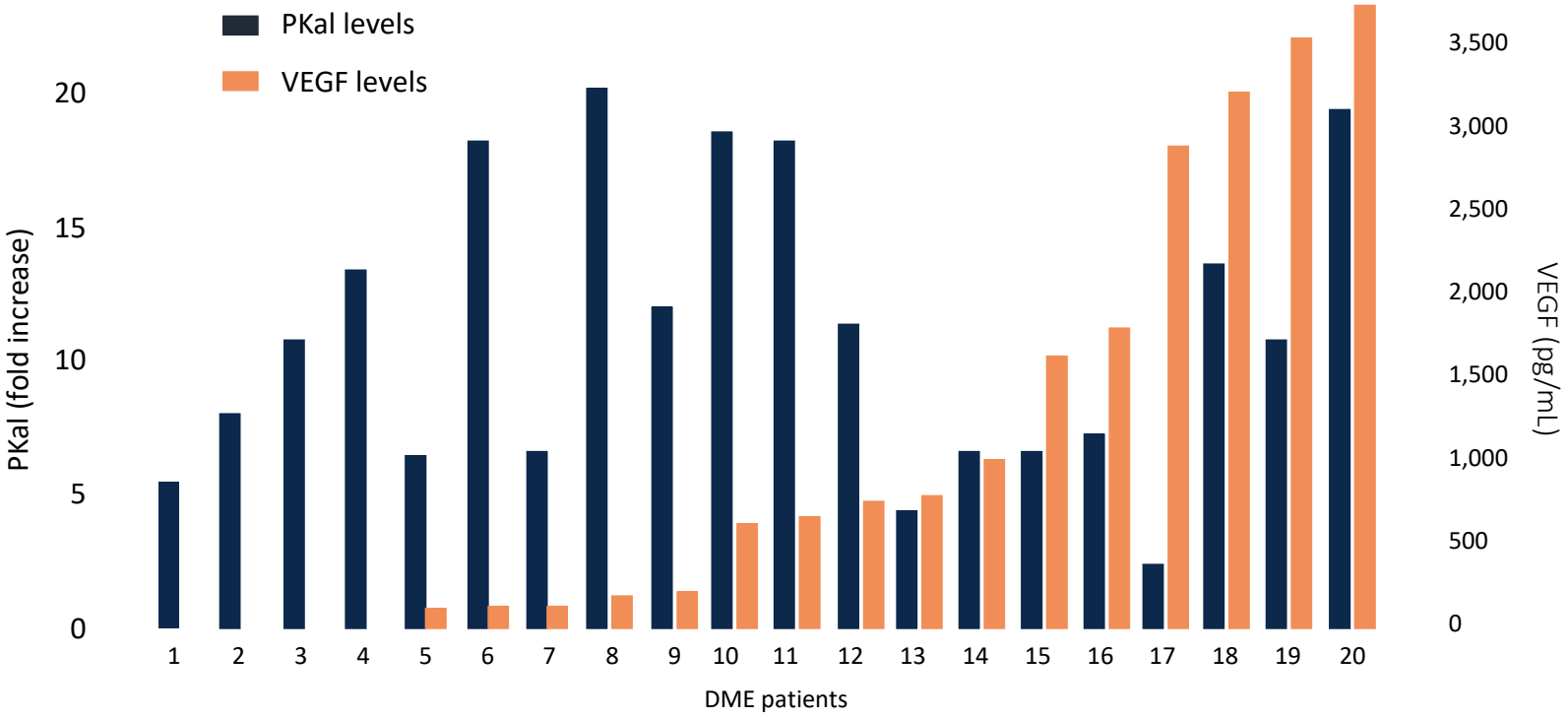

- By releasing the inflammatory hormone Bradykinin (BK) in response of a vascular injury, the Kallikrein-Kinin system (KKS) is a major driver in DME
- THR-149 is a **peptide** (1683 Da) in a **constrained bicyclic structure,** designed to confer **higher stability, affinity and selectivity** compared to the corresponding linear peptide
- **High potency: sub-nanomolar $K_i$ (inhibition constant) values (0.2 nM) against human Plasma kallikrein**
- THR-149 was developed by Oxurion in partnership with Bicycle Therapeutics

Teufel et al. *J Med Chem* 2018;61(7):2823-2836

Abbreviation(s): BK, bradykinin; DME, diabetic macular edema; FXII, factor XII; KKS, kinin kallikrein system; PK, PreKallikrein; PKal, plasma kallikrein

# Rationale for targeting Plasma Kallikrein in DME patients

## Pkal and VEGF: Two different pathways linked to DME

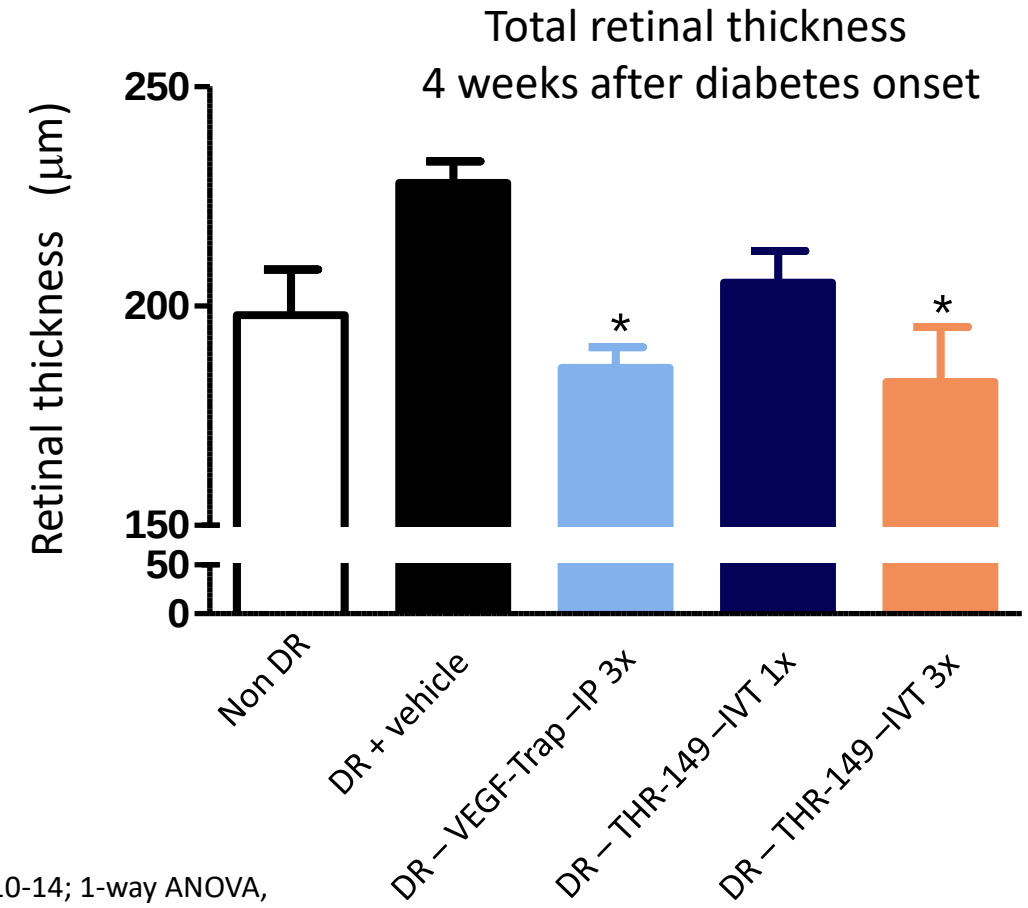



- Not all DME patients have increased VEGF levels
- Pkal levels are increased in DME patients
- PKal inhibitors have the potential as stand-alone therapy for sub-optimal responders to SOC, or for use in combination

Note: graph adapted from Kita et al. Diabetes 2015;64:3588-3599

Abbreviation(s): DME, diabetic macular edema; PKal, plasma kallikrein; VEGF: vascular endothelial growth factor; SOC: standard of care

# THR-149 • Total retinal thickness in diabetic rats: single vs. repeated injection



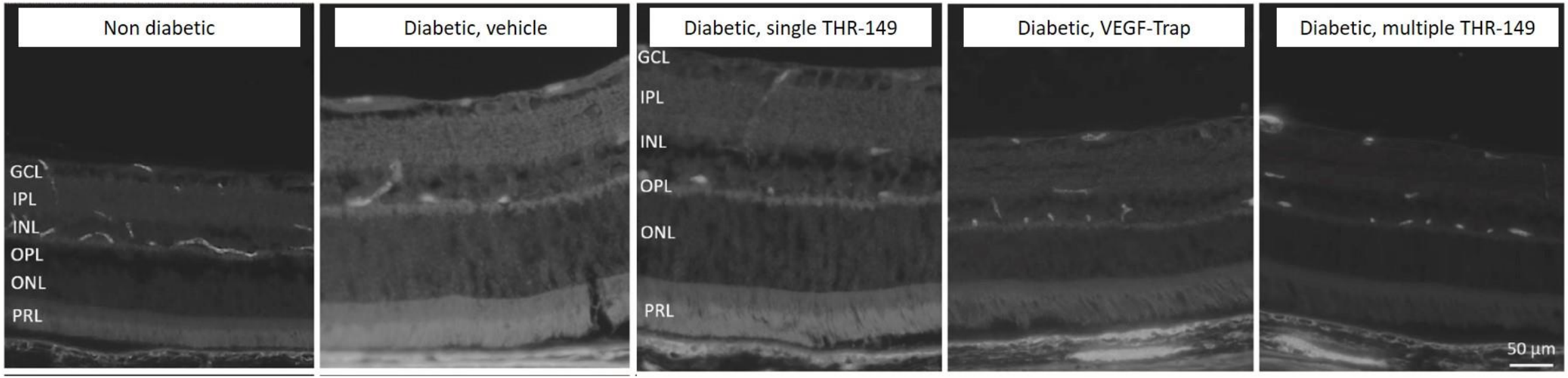

- **Multiple THR-149 IVT injections significantly reduce retinal thickness** by 50 µm ($p<0.05$) versus vehicle-treated eyes in the STZ diabetic rat, while single THR-149 IVT did not have a significant impact

Mean ± SEM; N=10-14; 1-way ANOVA,
* $p<0.05$ (*vs*. vehicle)
THR-149, 12.5 µg/eye IVT / week
VEGF-Trap, 2mg/kg IP / week

Abbreviation(s): STZ, streptozotocin; DR, diabetic retinopathy; IVT intravitreal; IP, intraperitoneal

# THR-149 • Total retinal thickness: single vs. repeated injection

Multiple THR-149 IVT injections reduce the thickness of specific retinal layers in the STZ diabetic rat
Single THR-149 IVT injection had no significant impact




- Repeat administration of THR-149 results in significant reduction ($p<0.01$) for the inner plexiform layer (IPL), inner nuclear layer (INL), outer nuclear layer (ONL) , and photoreceptor layer (PRL)

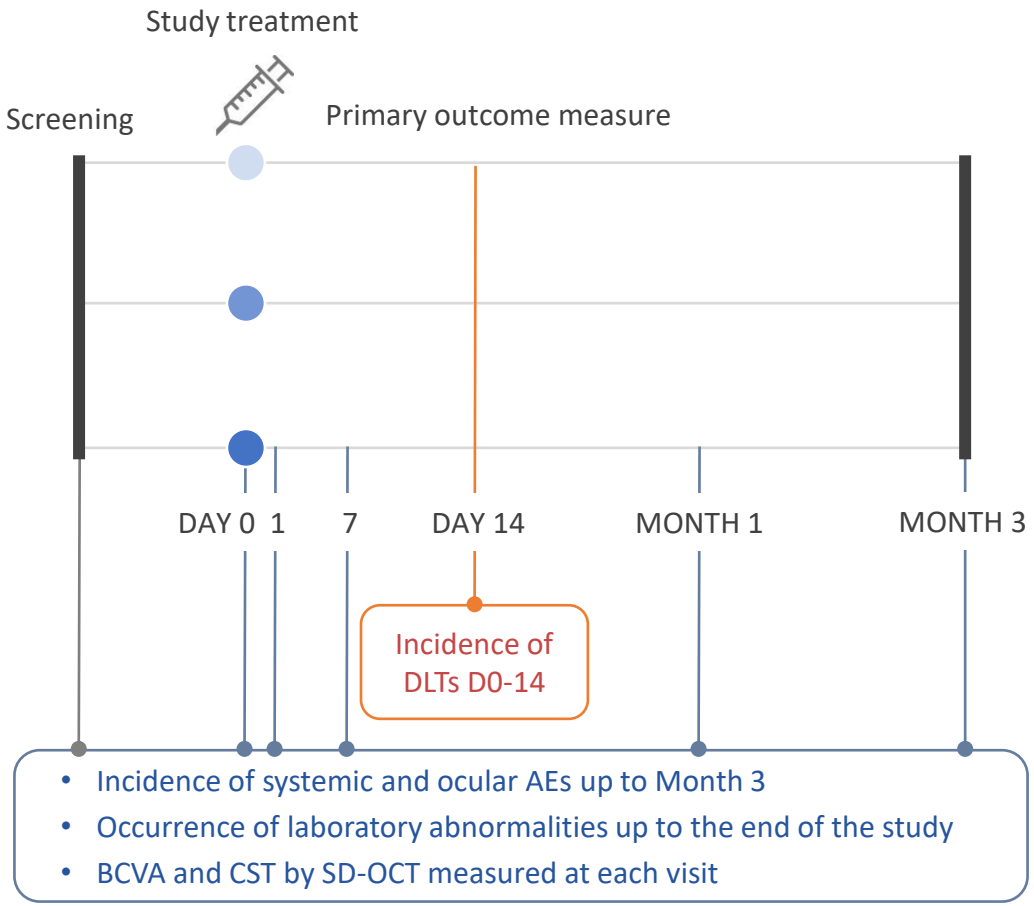
Abbreviation(s): STZ, streptozotocin; IVT, intravitreal; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PRL, photoreceptor layer

# THR-149-001: Phase 1 study design in DME patients

## 3+3 Dose-Escalation Study

**Total N = 12 patients**

- IVT administration
- Age > 18 years
- Center-involved DME; CST > 320 µm (SD-OCT)
- BCVA ≤ 62 and ≥ 23 letters
- History of response to prior anti-VEGF / corticosteroid treatment




Secondary outcome measures

- Incidence of systemic and ocular AEs up to Month 3
- Occurrence of laboratory abnormalities up to the end of the study
- BCVA and CST by SD-OCT measured at each visit

- 0.005 mg THR-149 (low dose)
- 0.022 mg THR-149 (middle dose)
- 0.130 mg THR-149 (high dose)

**DLT criteria**

- Intraocular inflammation: ≥ 2+ inflammation on any of intraocular inflammation grading scales
- BCVA: ≥ 10 ETDRS letter score decrease in BCVA from baseline

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; DLT, dose-limiting toxicity; DME, diabetic macular edema; ETDRS, early treatment diabetic retinopathy study; IVT, intravitreal; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor

# THR-149-001: Safety and preliminary efficacy results

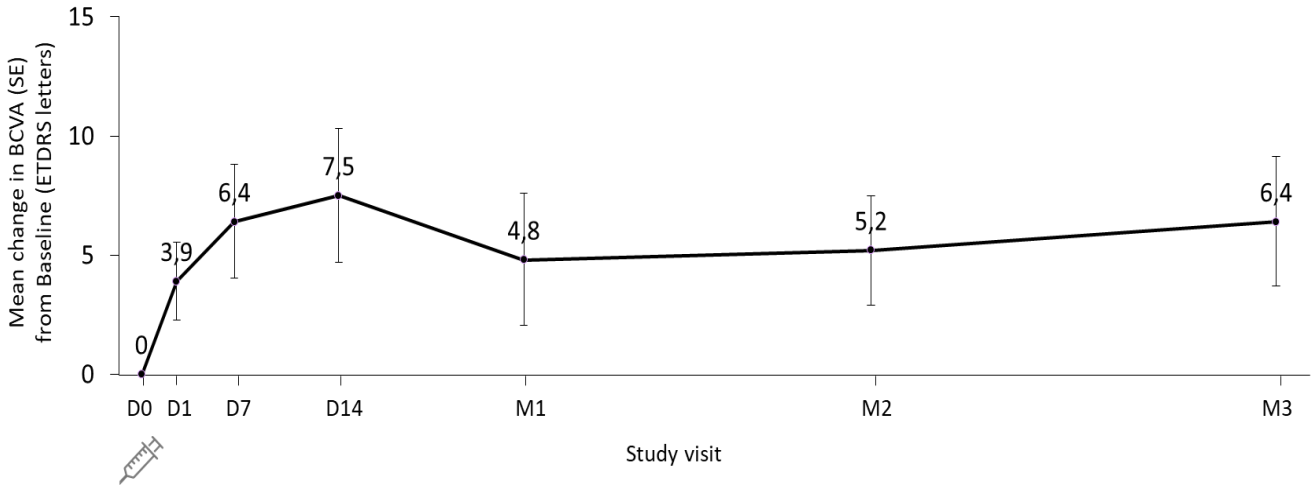
## All Treated Subjects, overall (n=12)

### Safety

- No DLTs (dose limiting toxicities) were noted at any dose
- 3 non-ocular, non-treatment-related SAEs developed in 1 subject
- 1 treatment-related AE was recorded in the study eye in 1 subject[a]

### Preliminary efficacy

- Mean BCVA[b] increased rapidly following the injection, peaking at 7.5 letters at Day 14 with gains maintained at 6.4 letters at Month 3
- Reductions in CST after 1 injection were marginal (not shown)




[a] Anterior chamber inflammation in the study eye, (verbatim term: 1+ anterior chamber inflammation) starting at D1 and resolved by D5

[b] Accounted for rescue: value before rescue carried forward

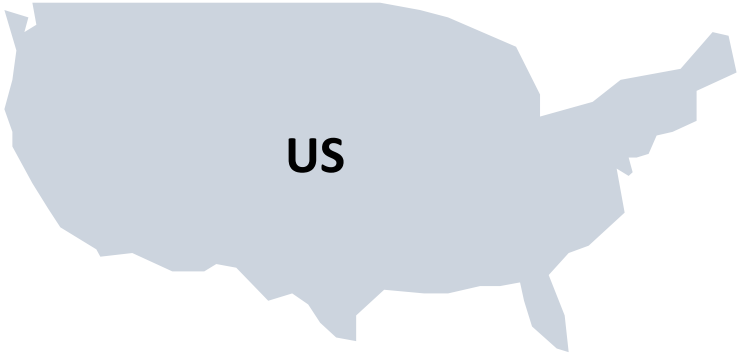
Abbreviations: BCVA, best-corrected visual acuity; D, day; ETDRS, early treatment diabetic retinopathy study; M, month; SE, standard error; CST, central subfield thickness; SAEs, serious adverse events;

# THR-149-002 KALAHARI trial

## Study sites in US and Europe

- Phase 2, multicenter, randomized, 2-part study
- 3 monthly injections
- 122 patients (anti-VEGF suboptimal responders)
  - Part A (N=18): select the dose of THR-149
  - Part B (N=104): compare THR-149 to aflibercept
- Primary Endpoint: BCVA – Secondary Endpoints: CST, AEs

- **Study timelines**
  - Part A: recruitment completed ✓
  - Dose selection: Sept 2021
  - Part B Topline data: H1 2023

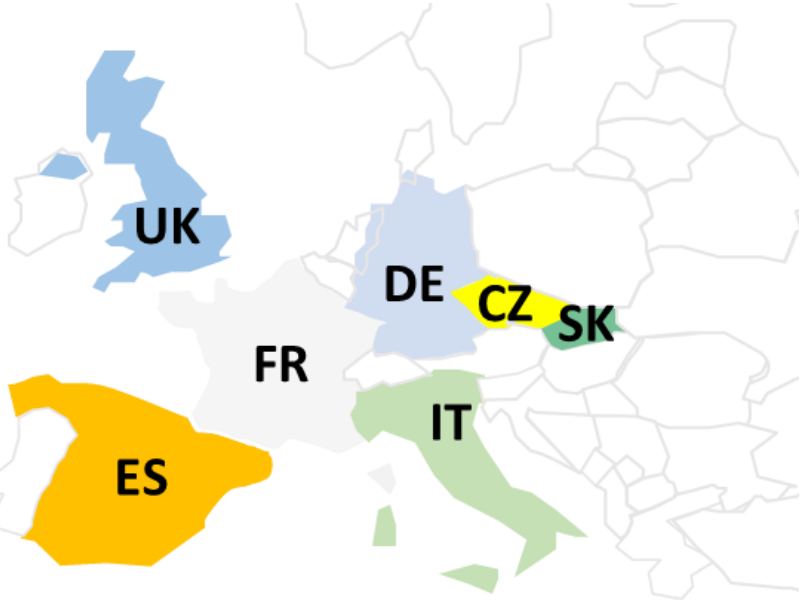



**Anti-VEGF suboptimal responders:**

Center-involved DME;
CST ≥ 320 µm (OCT)

BCVA ≤ 73 and ≥ 39 letters

≥ 5 anti-VEGF injections




Abbreviation(s): BCVA, best corrected visual acuity; CST, central subfield thickness; AEs, Adverse Events