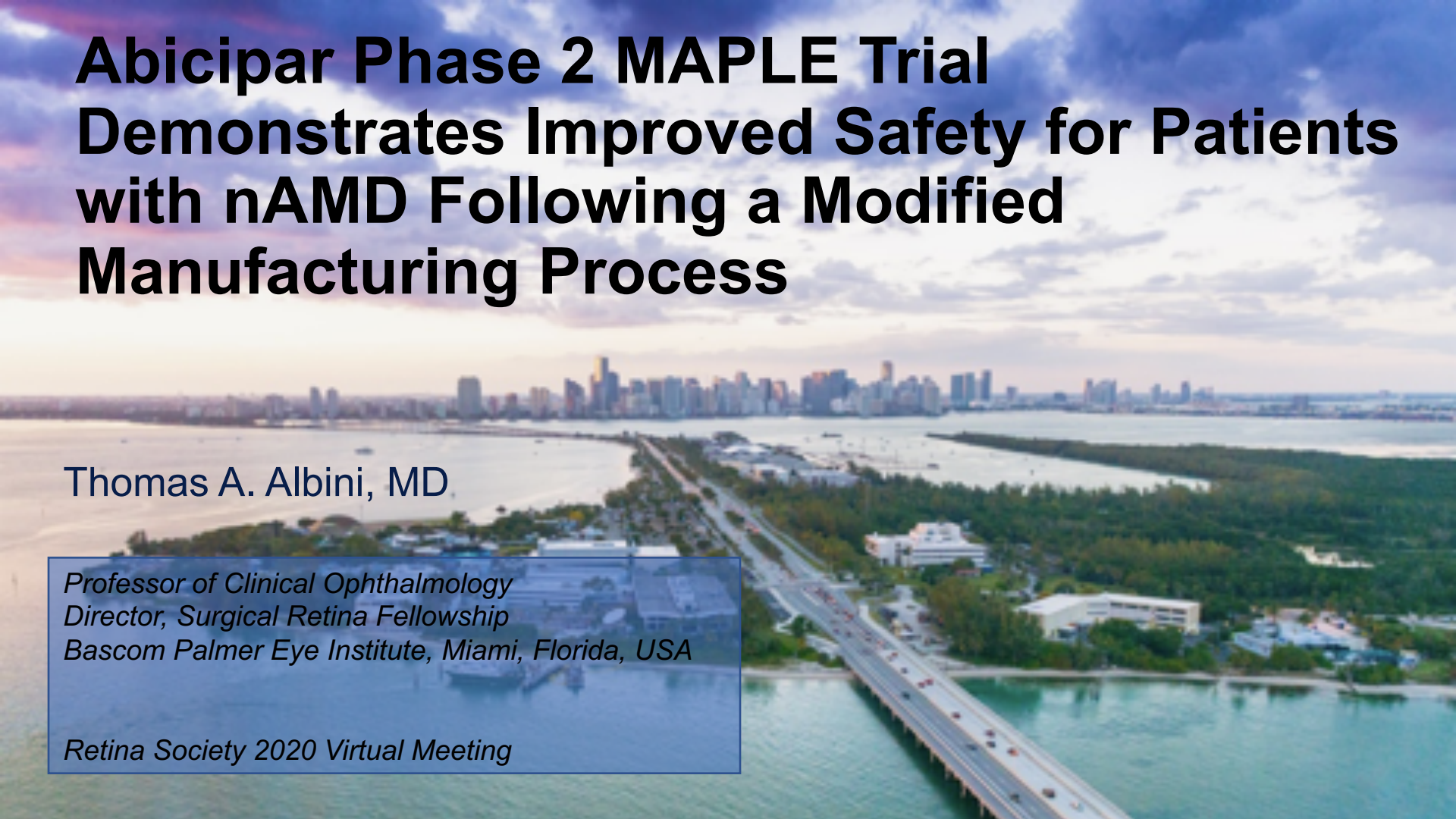
Abicipar Phase 2 MAPLE Trial Demonstrates Improved Safety for Patients with nAMD Following a Modified Manufacturing Process



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Disclosures

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- Consultant: Adverum, Allegro, Allergan (an AbbVie company), Beaver Visitec, Clearside, Eyepoint, Genentech, Janssen, Notal Vision, Novartis, RegenexBio, Santen, Valeant

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Summary

- DARPins are synthetic binding proteins that have high-binding affinity, a molar dose that can be engineered, and are customizable
- Abicipar pegol is a pegylated DARPin molecule with a molecular weight of 34 kDa that binds all soluble isoforms of VEGF-A with high affinity, long half life, and high molar dose
- CEDAR and SEQUIOA were pivotal trials that showed intravitreal abicipar every 8 weeks or 12 weeks had non-inferior visual outcomes compared to ranibizumab every 4 weeks
  - Subretinal fluid and intraretinal fluid resolved more rapidly with abicipar than ranibizumab
- Intraocular inflammation (IOI) was a key safety finding in CEDAR and SEQUOIA, with incidence at 1 year of 15.4% and 15.3% for abicipar Q8 and Q12 respectively
- MAPLE study using abicipar with an improved manufacturing process reduced inflammation to 8.9% at 28 weeks with good outcomes in eyes with IOI

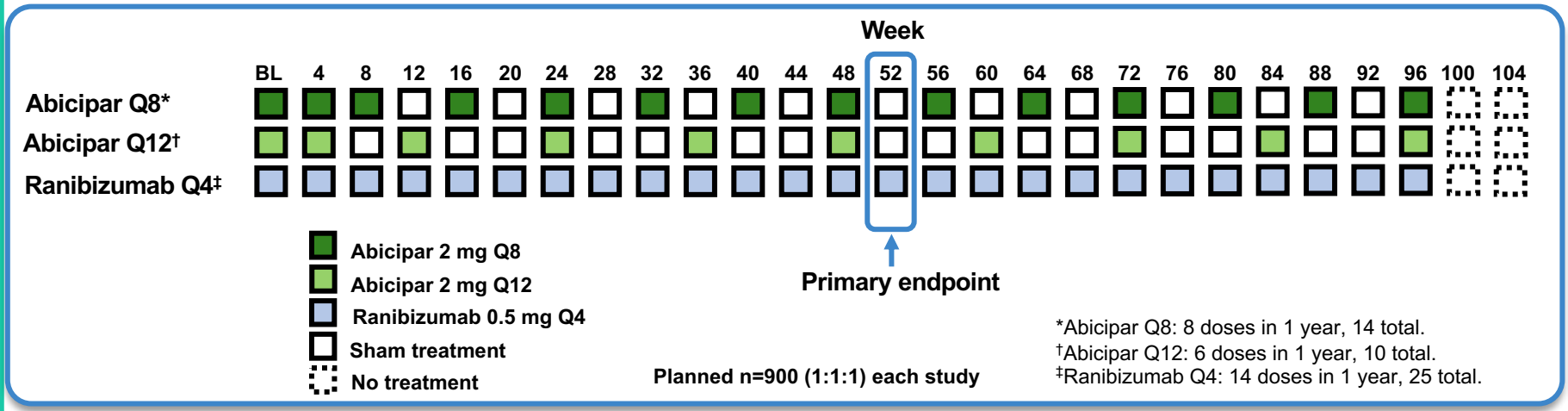
Phase 3 CEDAR and SEQUOIA Study Design

Two randomized, double-masked, parallel-group, clinical trials with identical protocols

Objective: To assess the safety and efficacy of abicipar pegol (abicipar) compared with ranibizumab in treatment-naïve patients with nAMD

Primary endpoint: Proportion of patients with stable vision (loss of < 15 ETDRS letters compared with baseline) at Week 52

Secondary Endpoint: Mean change from baseline in ETDRS BCVA, mean change from baseline in CRT, and proportion of patients with ≥ 15-letter gain at Week 52

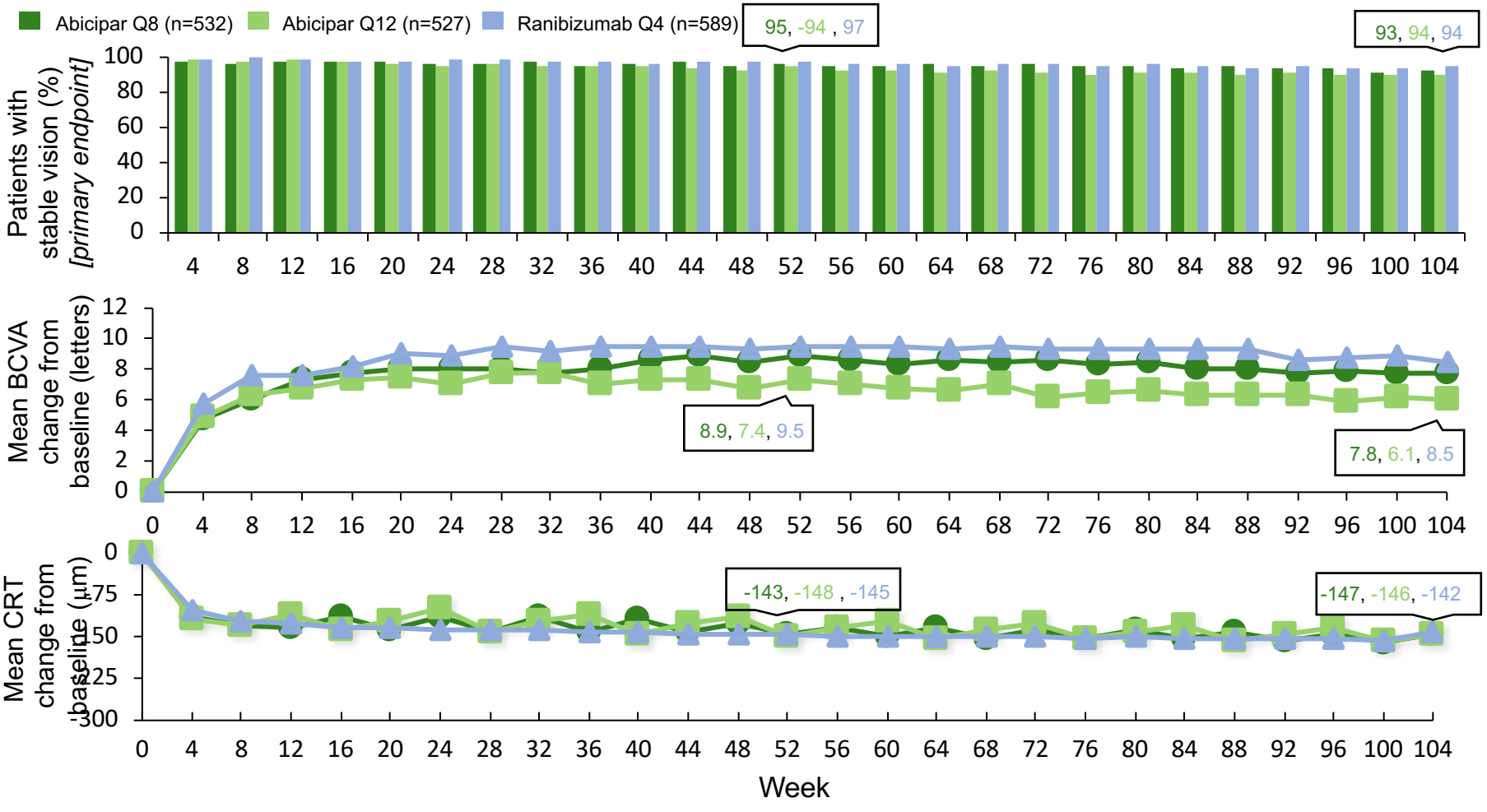


BCVA, best-corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration

Results

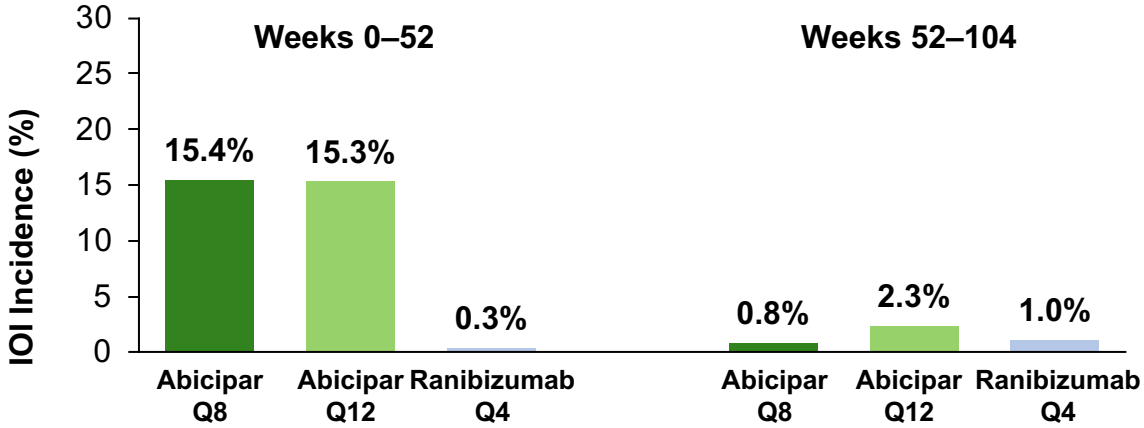
Abicipar Q8 and Q12 Noninferior to Ranibizumab

CEDAR SEQUOIA



Treatment-Emergent Adverse Events (TEAEs) and Intraocular Inflammation (IOI) in Year 1[1] and Year 2[2]

Adverse Event, n (%)	Abicipar Q8 (n=625) n (%)	Abicipar Q12 (n=626) n (%)	Ranibizumab Q4 (n=625) n (%)
Treatment-related TEAEs	237 (37.9)	257 (41.1)	196 (31.4)
Ocular	232 (37.1)	253 (40.4)	190 (30.4)
Study drug	110 (17.6)	141 (22.5)	40 (6.4)
Study procedure	171 (27.4)	184 (29.4)	177 (28.3)
Serious TEAEs	92 (29.5)	102 (32.7)	95 (30.6)



In Year 2, abicipar had:

- Comparable risk of IOI to ranibizumab
- No new cases of retinal vasculitis
- No new cases endophthalmitis

1. Khurana RN, et al. Presented at AAO 2018 Annual Meeting in Chicago, IL, USA; Oct 27-30, 2018. 2. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

Abicipar Safety: Year 1

Adverse Events of Intraocular Inflammation (IOI) by Maximum Severity

IOI AE Severity, n (%)	Abicipar Q8 (n=625)	Abicipar Q12 (n=626)	Ranibizumab Q4 (n=625)
Overall IOI rate	96 (15.4)	96 (15.3)	2 (0.3)
Mild/moderate	73%	76%	2 (0.3)
Severe	23 (3.7)	20 (3.2)	0

Definitions of AE severity:

- Mild – awareness of a sign or symptom, but easily tolerated
- Moderate – discomfort enough to cause interference with usual activity
- Severe – incapacitating with inability to work or do usual activity

>91% of IOIs occurred within the first 4 injections for Q12

Background

Biologics and Intraocular Inflammation (IOI)

A potential risk of biologics is that they introduce host cell-derived protein impurities in medications and can stimulate inflammation

- Bevacizumab reported incidence of IOIs = 1.3 % after 693 injections[1]
- Aflibercept – 41 cases of sterile endophthalmitis reported between 12/11 and 6/13[2]
- Brolucizumab – 36 cases of retinal vaculitis +/- vascular occlusion in Hawk & Harrier[3]
- APL-2 – several cases of noninfectious endopththalmitis in Phase 3 trials[4]
- Ranibizumab – Phase ½ FOCUS trial reported IOI with 38.1% of injections[5]; IOIs dramatically decreased in the Phase 3 trials after changing to a solubilized formulation[6]

1. Johnson D, et al. 2010. *Canadian J Ophthalmol*. 2010;45:239-242. 2. American Society of Retina Specialists (ASRS) Therapeutic Surveillance Committee 3. Novartis Safety Review Committee & Data Monitoring Committee Reports, made public June 2020 4. Apellis – Voluntary pause; impurities introduced during manufacturing scale-up to produce commercial lot sizes. 5. Spitzer MS, et al. *Clin Ophthalmol*. 2008;2:1-14. 6. Chong DY, et al. Retina. 2010;30:1432-1440.

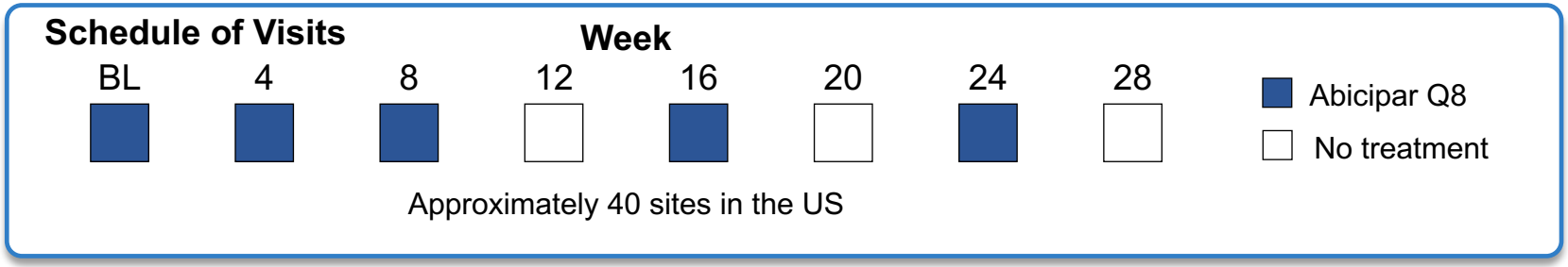
Abicipar: Modified Manufacturing Process

- Optimized for **REMOVAL** of host-derived impurities and specifically host cell proteins
- Enabled by development of sophisticated analytical and purification methods

MAPLE Study Design

Open-label, prospective, clinical trial

Objective: To evaluate the safety and treatment effect of intravitreal abicipar pegol produced using a modified manufacturing process



ClinicalTrials.gov Identifier: NCT03539549

BL, baseline; US, United States; VEGF, vascular endothelial growth factor

Treatment-Emergent Adverse Events (TEAEs) Summary

Adverse Event, n (%)	Abicipar Q8 (N=123)
TEAE	73 (59.3)
Ocular	45 (36.6)
Nonocular	55 (44.7)
Treatment-related TEAE	21 (17.1)
Ocular	20 (16.3)
Study drug-related	12 (9.8)
Study procedure-related	14 (11.4)
Nonocular	1 (0.8)
Serious TEAE	16 (13.0)
Death	2 (1.6)*
AE leading to study discontinuation	14 (11.4)

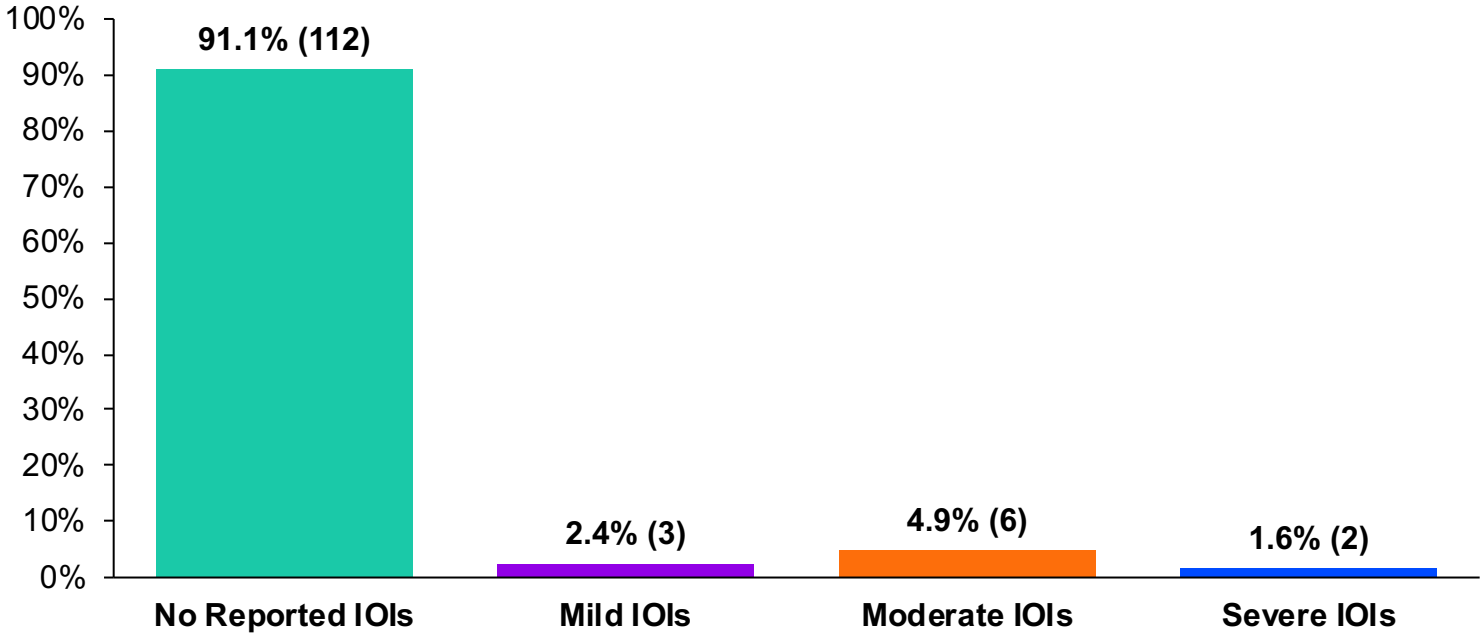
*Brain tumor; esophageal cancer

Treatment-Emergent Adverse Events of Special Interest in the Study Eye: Intraocular Inflammation

Preferred Term, n (%)	Abicipar Q8 (N=123)
Overall	11 (8.9)
Uveitis	3 (2.4)
Vitritis	2 (1.6)
Iridocyclitis	3 (2.4)
Iritis	3 (2.4)
Keratic precipitates	1 (0.8)
Vitreous haze	1 (0.8)

11 patients discontinued from the study; 2 patients were rated severe by the investigators.
No retinal vasculitis or endophthalmitis was reported.

Intraocular Inflammation (IOI) by Maximum Severity[a]



[a]Severity was reported according to investigator assessment

Results

All 11 Patients in MAPLE Trial With Intraocular Inflammation (IOI)

	Patient	Physician Classification	Most Severe AC Finding	Most Severe Posterior Finding	Steroid Treatment for IOI	BCVA at Baseline	BCVA at AE Start	BCVA at Last Visit	Outcome
Mild	1	Iritis*	+1 cells; +0.5 cells	None	Topical	77 (20/32)	NA	25 (20/320)	Resolved
	2	Anterior uveitis	+2 cells, +2 flare	+0.5 cells	Topical	50 (20/100)	NA	38 (20/200)	Resolved
	3	Vitritis	+0.5 cells	+2 cells	None	75 (20/32)	85 (20/20)	81 (20/25)	Resolved BCVA > baseline
	4	Iritis	+0.5 cells	+1 cells, +1 debris	Topical	72 (20/40)	77 (20/32)	76 (20/32)	Resolved BCVA > baseline
Moderate	5	Anterior uveitis	+1 cells, +1 flare	None	Topical	74 (20/32)	86 (20/20)	83 (20/25)	Resolved BCVA > baseline
	6	Anterior intermediate uveitis	+3 cells, +2 flare	+1 cells, +1 haze	Topical and oral	78 (20/32)	64 (20/50)	73 (20/40)**	Resolved**
	7	Panuveitis	+2 cells, +1 flare	None	Topical	68 (20/50)	64 (20/50)	74 (20/32)	Resolved BCVA > baseline
	8	Panuveitis (pan) and mild uveitis (uve)	+2 cells, +1 flare	None	Topical & subconj	75 (20/32)	83 (20/25)	83 (20/25)	Resolved BCVA > baseline
	9	Keratic precipitates and vitritis	None	+3 cells, +1 haze	Topical	67 (20/50)	66 (20/50)	69 (20/50)	Resolved BCVA > baseline
Severe	10	Iritis	+1 cells	+2 haze, +2 cells, +2 debris	Topical	52 (20/100)	40 (20/160)	55 (20/80)**	Resolved BCVA > baseline
	11	Panuveitis	+2 cells	Opacities	Topical and oral	71 (20/40)	NA	62 (20/63)**	Resolved**

NA = Not available/data pending; AC = anterior chamber; BCVA = best corrected visual acuity: in ETDRS (Snellen); AE = adverse event; With sequelae = BCVA did not resolve to baseline by study exit visit.

*Patient had 2 cases of iritis; **Beyond Week 28 visit.

In the Phase 3 Studies

- Visual gains at 1 year were as effectively maintained with 4 injections of abicipar as with 12 injections of ranibizumab during the second year
- BCVA and CRT improvement, maintained to Week 104, were similar on abicipar Q12 and ranibizumab
- Rate of IOI in Weeks 0–52 was 15.4%, 15.3%, and 0.3% in the abicipar Q8, abicipar Q12, and ranibizumab groups
- Over 90% of cases of IOI occurred with the first 4 injections of abicipar Q12
- The rate of IOI was comparable between treatment groups during Year 2

In the MAPLE Study

- Abicipar produced through a modified manufacturing process demonstrated an improved safety profile versus the phase 3 studies
  - The overall incidence of IOI (Baseline to Week 28) was 8.9% (Q8)
- Most IOIs were mild to moderate in severity and occurred within the first 4 injections
- No reported cases of endophthalmitis or retinal vasculitis
- Visual acuity in the majority of patients with IOIs recovered to baseline levels or better by the last visit

Conclusions

Take Home Messages

- DARPins are synthetic binding proteins that have high-binding affinity, a molar dose that can be engineered, and are customizable
- Abicipar pegol is a pegylated DARPin molecule with a molecular weight of 34 kDa that binds all soluble isoforms of VEGF-A with high affinity, long half life, and high molar dose
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