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Results From the SAKURA Program: Vitreous Haze Improvement With Intravitreal Sirolimus in Subjects With Non-infectious Uveitis of the Posterior Segment

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Background

- Intravitreal (IVT) sirolimus, a locally delivered inhibitor of mammalian target of rapamycin, a key driver of inflammation,[1] may be effective for non-infectious uveitis of the posterior segment (NIU-PS).
- The SAKURA Program is comprised of two multinational Phase III double-masked randomized clinical trials, SAKURA 1 and SAKURA 2, assessing the efficacy and safety of every-other-month IVT sirolimus in subjects with active NIU-PS.[2]
- The SAKURA Program, which enrolled 592 subjects, is the largest study of NIU-PS to date.

Objective

- To assess the effect of IVT sirolimus on vitreous haze (VH) in the SAKURA program.

Methods

- Subjects with active NIU-PS and baseline VH ≥1.5+ in the study eye who fulfilled inclusion criteria were randomized 1:1:1 to IVT sirolimus 44 µg (active control), 440 µg, or 880 µg administered every-other-month.
- Investigation of the 880 µg dose was terminated after SAKURA 1 showed that the 440 µg dose had a more favorable benefit:risk profile.
- VH was assessed at Week 2 and then monthly between Months 1–5. Scores ranged from 0 (no inflammation) to 4+ (severe inflammation).
- Primary endpoint: VH=0 in the study eye at Month 5.
- Adverse events (AEs) were assessed through Month 6.

Results

- The integrated intent-to-treat (ITT) population comprised 208 subjects in each of the 44 µg and 440 µg dose groups. Demographic and baseline characteristics are summarized in **Table 1**.

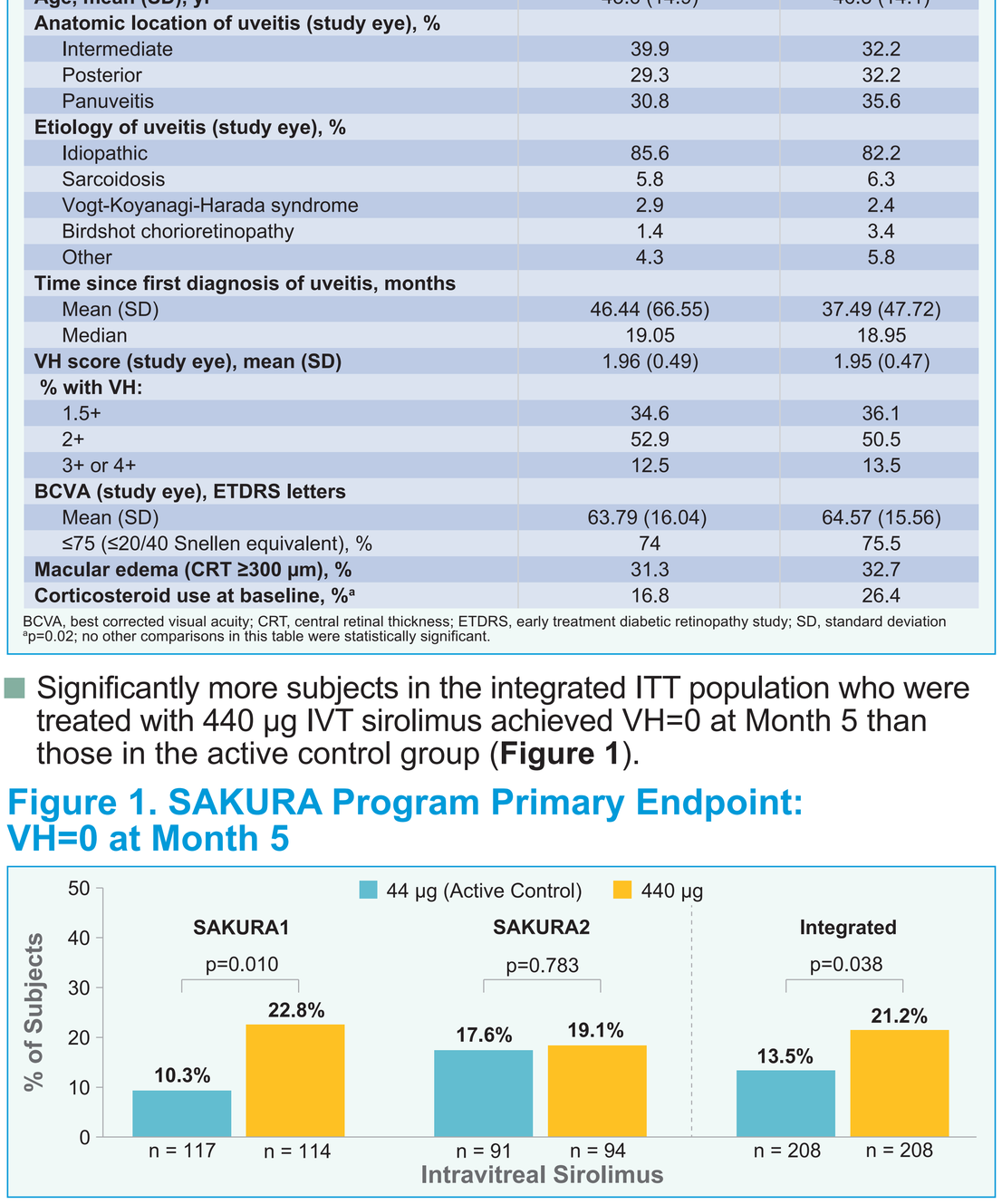
Table 1. Demographics and Baseline Characteristics of the Integrated Intent-to-treat Population

	Intravitreal Sirolimus	
	44 µg (Active Control) (n = 208)	440 µg (n = 208)
Female, %	54.3	56.3
Age, mean (SD), yr	43.6 (14.9)	46.3 (14.1)
Anatomic location of uveitis (study eye), %		
Intermediate	39.9	32.2
Posterior	29.3	32.2
Panuveitis	30.8	35.6
Etiology of uveitis (study eye), %		
Idiopathic	85.6	82.2
Sarcoidosis	5.8	6.3
Vogt-Koyanagi-Harada syndrome	2.9	2.4
Birdshot chorioretinopathy	1.4	3.4
Other	4.3	5.8
Time since first diagnosis of uveitis, months		
Mean (SD)	46.44 (66.55)	37.49 (47.72)
Median	19.05	18.95
VH score (study eye), mean (SD)	1.96 (0.49)	1.95 (0.47)
% with VH:		
1.5+	34.6	36.1
2+	52.9	50.5
3+ or 4+	12.5	13.5
BCVA (study eye), ETDRS letters		
Mean (SD)	63.79 (16.04)	64.57 (15.56)
≤75 (≤20/40 Snellen equivalent), %	74	75.5
Macular edema (CRT ≥300 µm), %	31.3	32.7
Corticosteroid use at baseline, %[a]	16.8	26.4

BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, early treatment diabetic retinopathy study; SD, standard deviation
[a]p=0.02; no other comparisons in this table were statistically significant.

- Significantly more subjects in the integrated ITT population who were treated with 440 µg IVT sirolimus achieved VH=0 at Month 5 than those in the active control group (**Figure 1**).

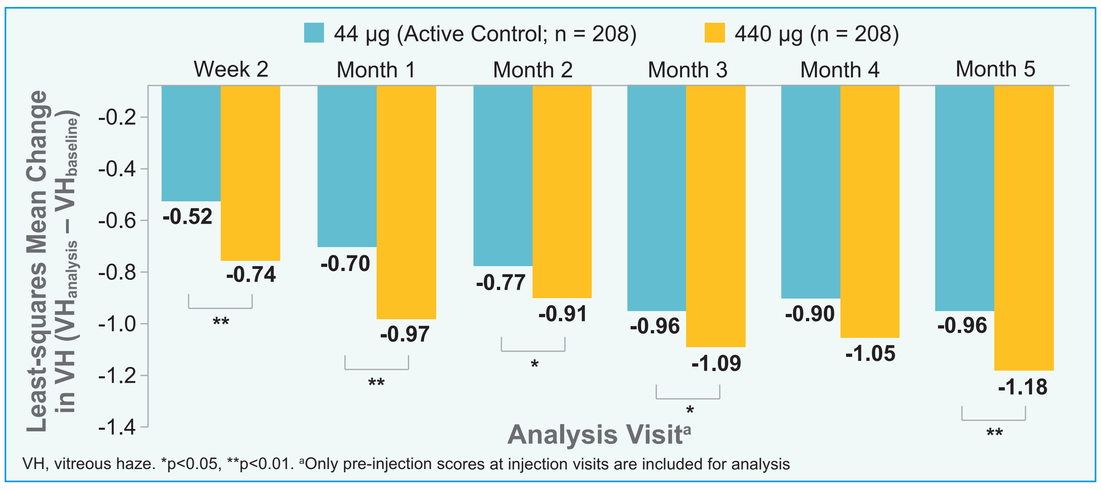
Figure 1. SAKURA Program Primary Endpoint: VH=0 at Month 5



Results (continued)

- At all but one analysis time (Month 4), the mean change in VH from baseline was significantly greater in the 440 µg dose group than in the active control group (**Figure 2**).

Figure 2. SAKURA Program Secondary Endpoint: Change in Vitreous Haze Over Time in the Study Eye



VH, vitreous haze. *p<0.05, **p<0.01. [a]Only pre-injection scores at injection visits are included for analysis

- The frequency of non–inflammation-related ocular serious AEs in the study eye was similar in all dose groups, but inflammation-related events were more common in the 880 µg group (**Table 2**).

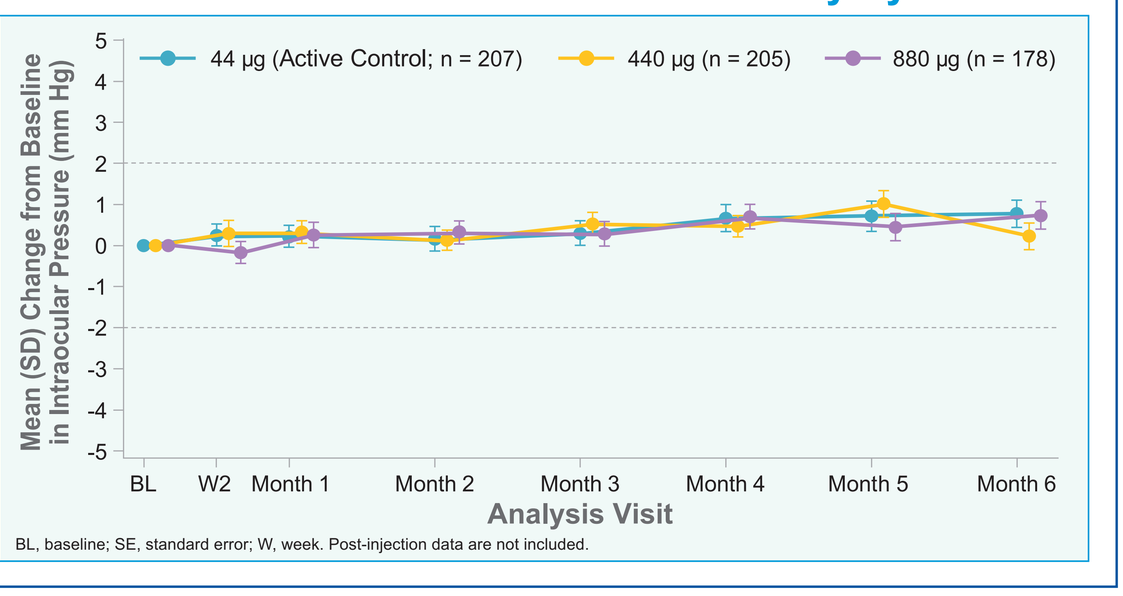
Table 2. Serious Adverse Events in the Study Eye

	Intravitreal Sirolimus		
	44 µg (n = 207)	440 µg (n = 205)	880 µg (n = 178)
Subjects with any serious ocular adverse event	29 (14.0%)	34 (16.6%)	36 (20.2%)
Worsening uveitis[a]	14 (6.8%)	15 (7.3%)	17 (9.6%)
Sterile endophthalmitis	0	1 (0.5%)	7 (3.9%)
Endophthalmitis	0	1 (0.5%)	1 (0.6%)
Transient drug depot in visual axis	2 (1.0%)	2 (1.0%)	4 (2.2%)
Increased intraocular pressure	2 (1.0%)	3 (1.5%)	2 (1.1%)
Cataract	2 (1.0%)	1 (0.5%)	3 (1.7%)
Retinal detachment	2 (1.0%)	1 (0.5%)	0

[a]Includes uveitis, choroiditis, iridocyclitis, vitritis, and intermediate uveitis.

- No clinically significant changes in intraocular pressure (IOP) were observed (**Figure 3**). At Week 2, the mean (SD) changes from baseline in the 44 µg and 440 µg dose groups were 0.3 (3.8) mmHg and 0.3 (4.6) mmHg, respectively. At Month 5, these changes were 0.7 (5.1) mmHg and 1.0 (4.5) mmHg, respectively.

Figure 3. SAKURA Program: Mean Change From Baseline in Intraocular Pressure in the Study Eye



BL, baseline; SE, standard error; W, week. Post-injection data are not included.

Conclusions

- In the integrated ITT population, subjects with NIU-PS who were treated with 440 µg IVT sirolimus had significantly greater improvements in VH than those treated with the 44 µg active control dose.
- Ocular serious AEs were generally manageable and consistent with those associated with IVT therapy. Of note, IOP did not change significantly in either dose group.
- The SAKURA Program demonstrates that repeated administrations of IVT sirolimus lead to improvement in ocular inflammation in subjects with active NIU-PS.

References: 1. Nguyen QD et al. *J Ophthalmic Inflamm Infect.* 2013;3:32. **2.** Santen, Inc. Summary of Clinical Efficacy 2.7.3. January 2017.
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