Baseline Factors Associated With No Improvement in Diabetic Retinopathy Severity Scale Score in Sham Patients From PANORAMA Over 2 Years

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PANORAMA Study Design

Phase 3, double-masked, randomized study of IAI efficacy and safety in patients with moderately severe to severe NPDR (DRSS level 47 and 53)
N=402[a]

- **Sham** n=133
- **IAI 2q16[b]** n=135
- **IAI 2q8/PRN[c]** n=134

Week 24
Primary endpoint: Proportion of patients improving ≥2 steps on DRSS
All IAI combined versus sham

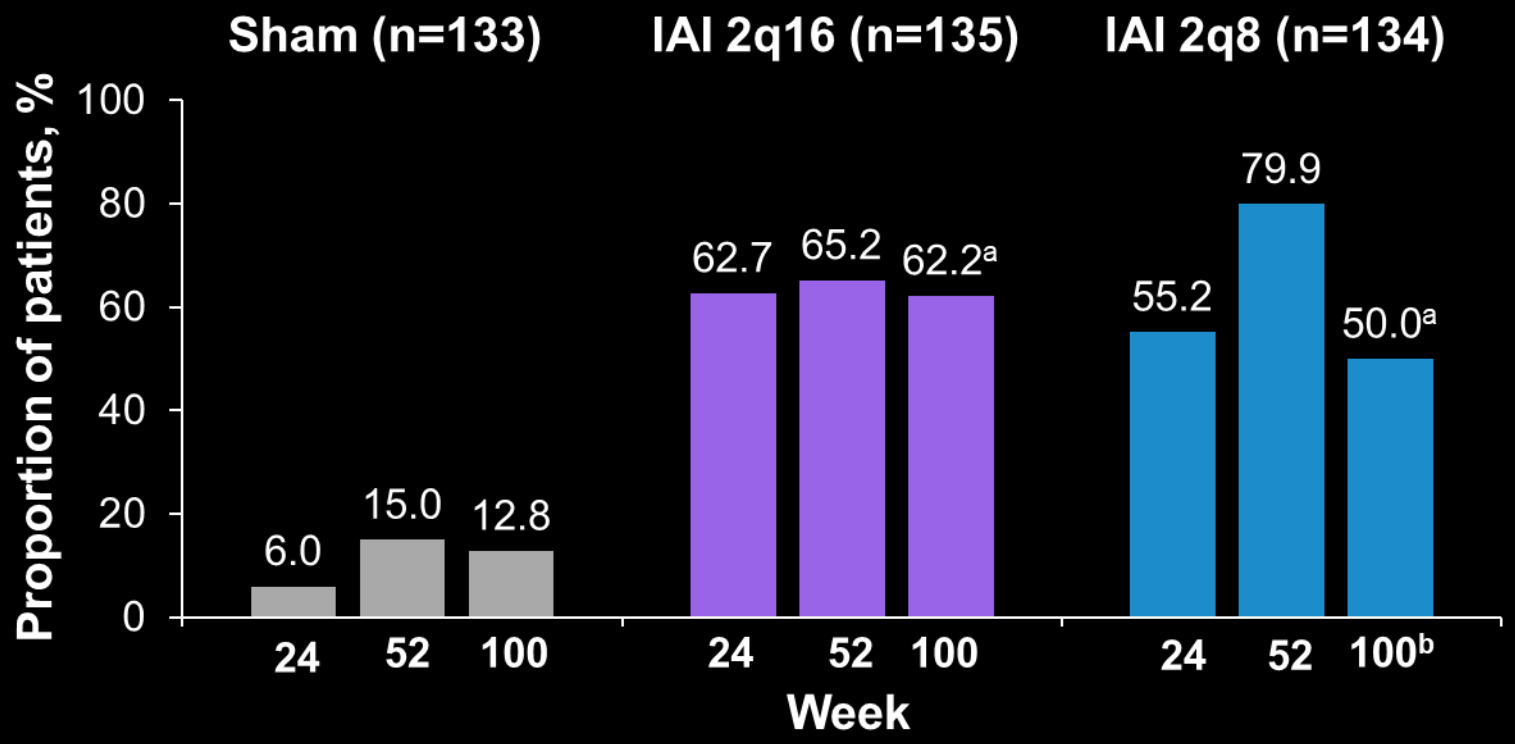
Week 52
Primary endpoint: Proportion of patients improving ≥2 steps on DRSS
IAI 2q16 and 2q8 individually versus sham

Follow-up through Week 100

Key Secondary endpoints
- % developing PDR/ASNV
- % developing CI-DME
- Time to development of PDR/ASNV or CI-DME

[a]Patients were stratified by baseline DRSS level. [b]After 3 initial monthly doses and one 8-week interval. [c]Patients received IAI 2q8 after 5 initial monthly doses through Week 52, followed by flexible treatment from Week 52 through Week 100.
2q16, 2 mg every 16 weeks; ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; IAI, intravitreal aflibercept injection; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRN, pro re nata.
Brown DM et al. *JAMA Ophthalmol*. 2021;139:946–955.

Proportion of Patients with ≥2-Step DRSS Improvement from Baseline



In PANORAMA, 15% and 13% of patients in the sham group had a ≥2-step DRSS improvement from baseline at Week 52 and Week 100, respectively

[a]Nominal *P*<0.0001 versus sham.
[b]Independent reading center review of investigator PRN decisions suggests undertreatment during Year 2.

Background

- Some patients with DR may improve in severity spontaneously without intervention[1]
- Baseline factors predicting which patients are likely to improve or not improve in DR severity may help physicians to prioritize appropriate patients for closer monitoring and earlier treatment
- In PANORAMA, patients with moderately severe to severe NPDR received sham treatment for 2 years[2]
  - This provided an opportunity to evaluate the rates of spontaneous improvement and no improvement in DR severity and their associated baseline factors

This post hoc analysis of PANORAMA evaluated clinically relevant baseline factors associated with improvement vs no improvement in DRSS score in patients receiving sham treatment at Weeks 52 and 100

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, non-proliferative diabetic retinopathy.

1. Basurto A et al. *Can J Ophthalmol.* 2020;55:e92–e95; 2. Brown DM et al. *JAMA Ophthalmol.* 2021;139:946–955.

Methods

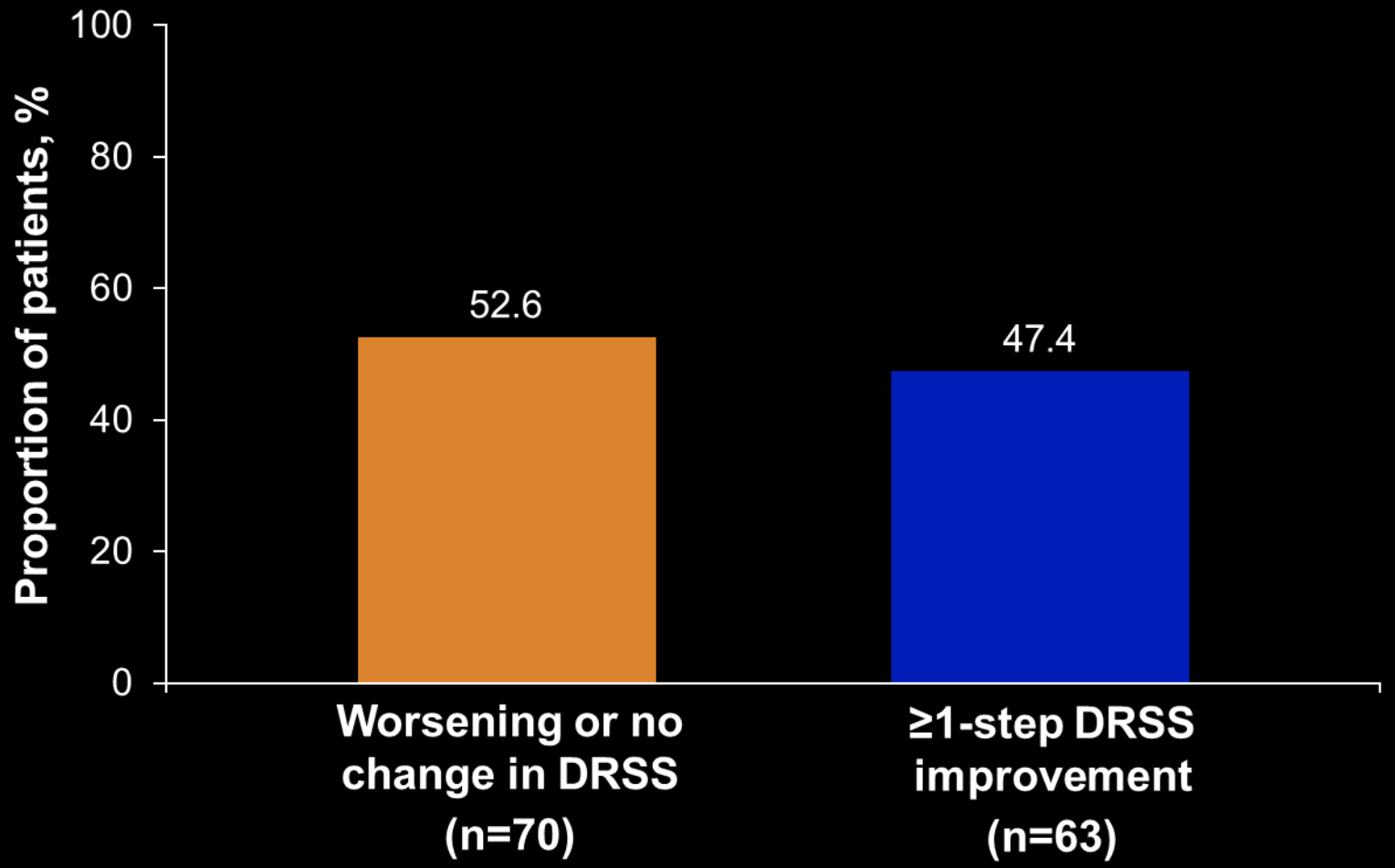
- Baseline factors were evaluated for association with no DRSS score improvement (worsening/no change) as well as ≥1-step DRSS improvement
- The baseline factors evaluated which were considered to be clinically relevant were patient characteristics, medical history, clinical and ocular characteristics, laboratory values, and medication use (including antihypertensives, lipid-lowering agents, and insulin)
- Univariate regression analysis adjusted for randomization strata evaluated the association of each baseline factor with DRSS score outcomes
- Multivariable analysis with stepwise regression was then performed using the factors that were identified in the univariate analysis
- Last observation carried forward was used. *P*-values were considered nominal and were not adjusted for multiplicity
- For any patient who received rescue treatment, data were censored from the time rescue treatment was given

Demographics and Clinically Relevant Baseline Factors

Patient characteristics	• Age • BMI • Ethnicity • Hemoglobin A1c • Race • Sex
Baseline medical history, clinical and ocular characteristics	• Diabetes duration • Diabetes type • Hypertension • Lipid disorder • BCVA • CST • Center subfield sector volume • DRSS score • Intraocular pressure • Leakage area • Leakage distance to fovea • Nonperfusion area
Microvascular or macrovascular complications	**Microvascular** • Diabetic nephropathy • Peripheral neuropathy **Macrovascular** • Coronary artery disease • Cerebrovascular disease • Peripheral arterial disease
Laboratory values	• Albumin • BUN • CrCl • Creatinine • Hematocrit • Hemoglobin • Platelets • 25-Hydroxyvitamin D • Urine protein, creatinine & ratio
Medication use	• Antihypertensives • Lipid-lowering agents • Insulin

BCVA, best-corrected visual acuity; BMI, body mass index; BUN, blood urea nitrogen; CrCl, creatinine clearance; CST, central subfield thickness.

Proportion of Patients in the Sham Group by DRSS Response at Week 52



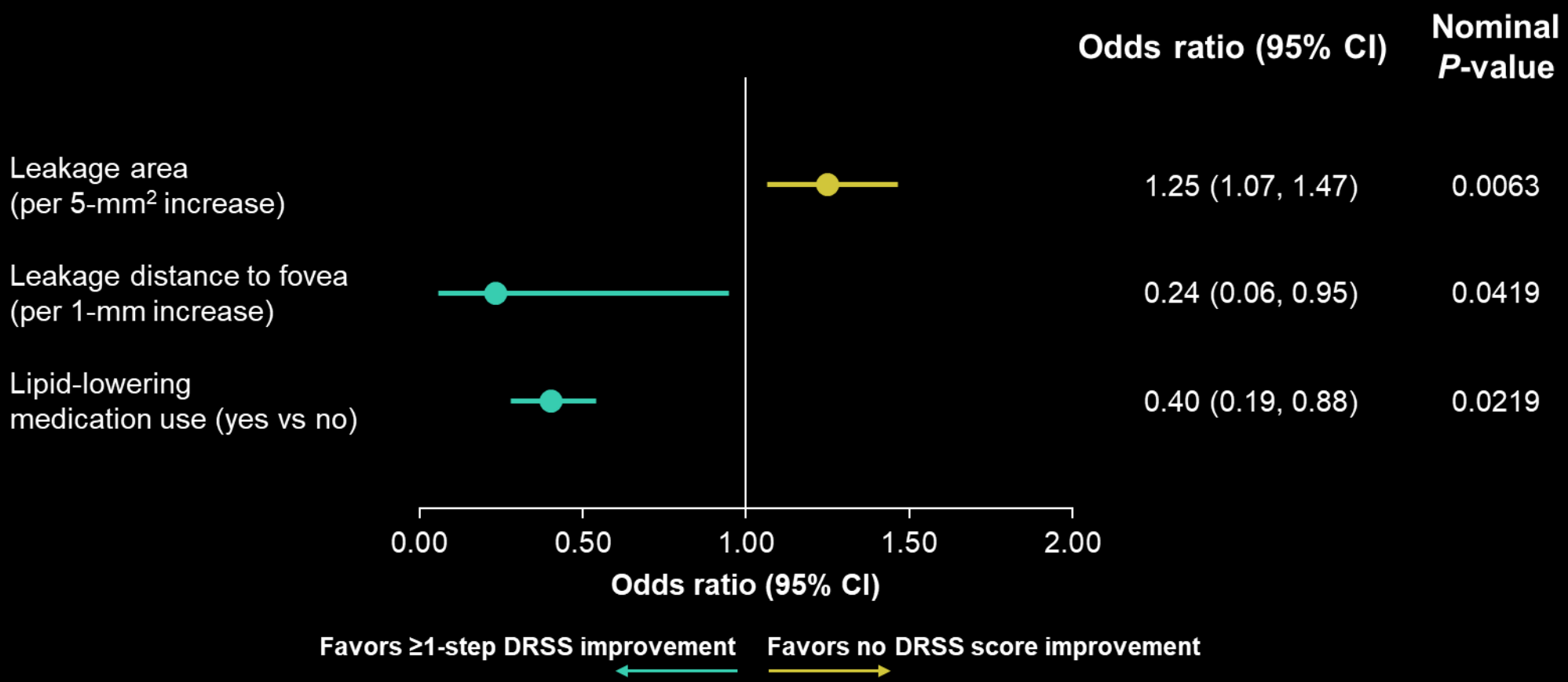
FAS, LOCF.
FAS, full analysis set; LOCF, last observation carried forward.

Baseline Characteristics by DRSS Response at Week 52 in Sham Patients

	Worsening or no change in DRSS (n=70)	≥1-step DRSS improvement (n=63)
Age, mean (SD), years	54.4 (11.1)	57.5 (9.2)
Female, n (%)	36 (51.4)	28 (44.4)
HbA1c, mean (SD), %	8.8 (1.7)	8.3 (1.4)
Type 2 diabetes, n (%)	63 (90.0)	60 (95.2)
Duration of diabetes, mean (SD), years	15.0 (8.4)	16.1 (10.3)
History of hypertension, n (%)	54 (77.1)	54 (85.7)
Lipid-lowering medication use, n (%)	40 (57.1)	49 (77.8)
ETDRS letter score, mean (SD)	82.7 (5.9)	82.8 (6.2)
DRSS score in study eye, n (%)		
47	50 (71.4)	49 (77.8)
53	20 (28.6)	14 (22.2)
CST, mean (SD), μm	254.2 (42.4)	244.0 (33.0)
Leakage area, mean (SD), mm^2	23.2 (11.7)	16.8 (11.5)
NP area, mean (SD), mm^2	0.4 (1.1)	0.3 (0.5)

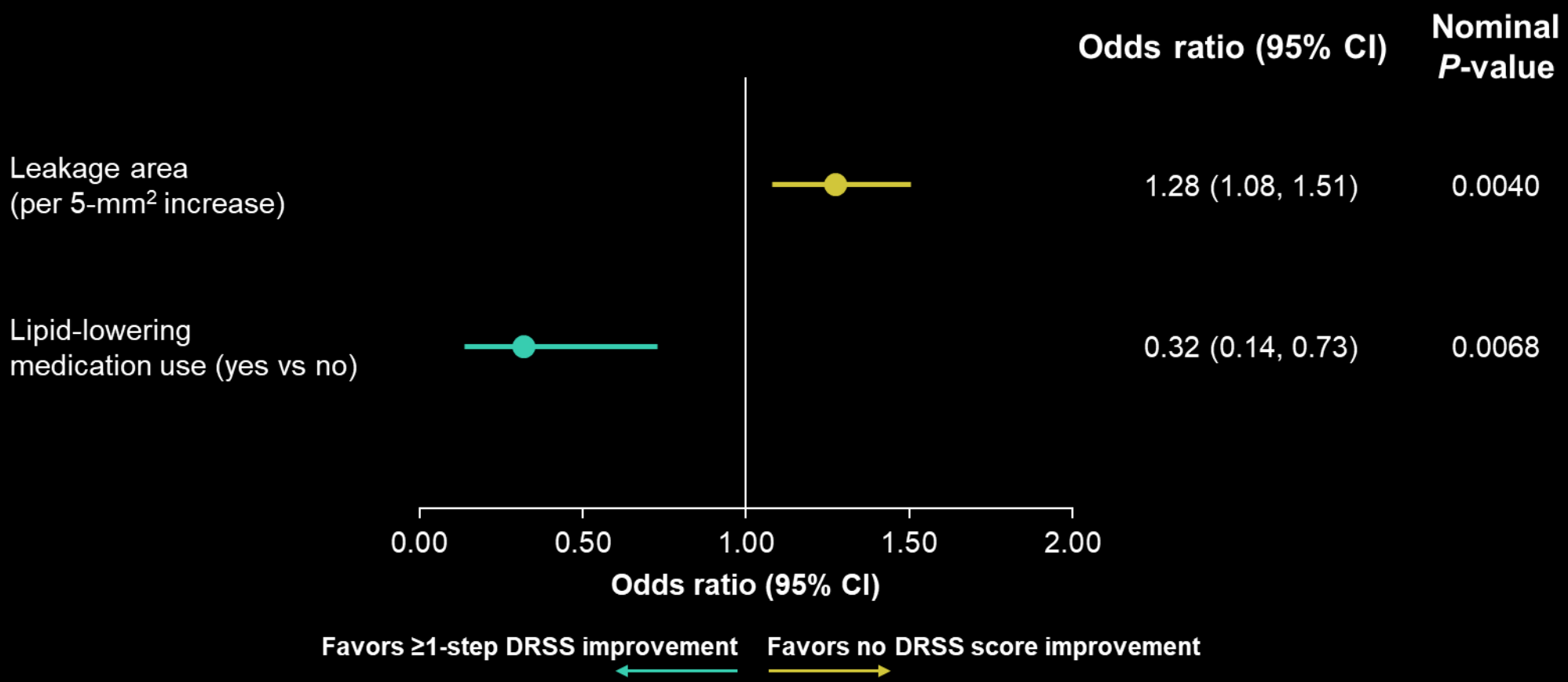
FAS, LOCF.
ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, hemoglobin A1c; NP, nonperfusion; SD, standard deviation.

Univariate Analysis: Baseline Factors Associated With No DRSS Score Improvement and ≥1-Step DRSS Improvement at Week 52



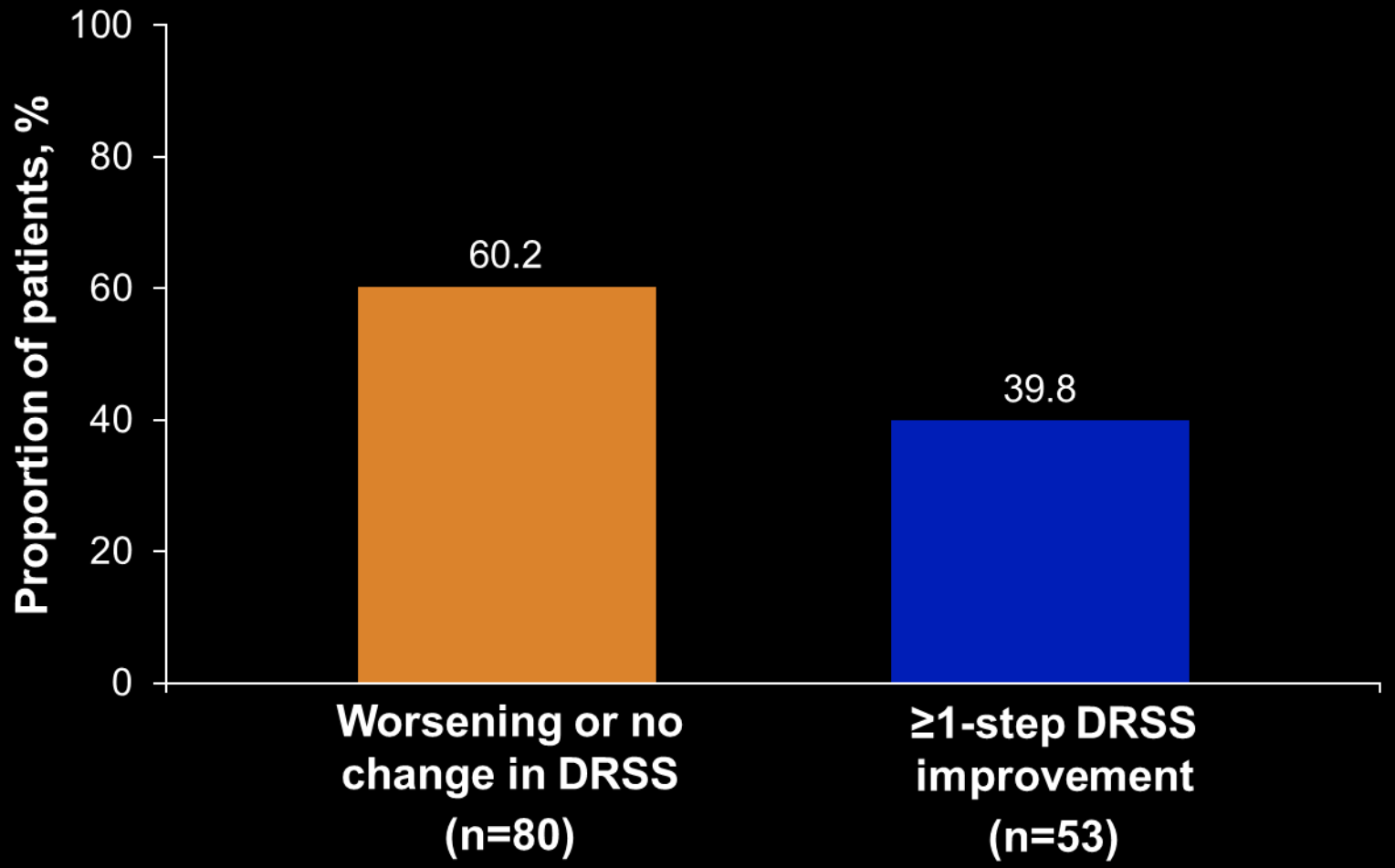
LOCF. Inferential results were derived from a logistic regression model adjusted for randomization strata.
CI, confidence interval; HR, hazard ratio.

Multivariable Analysis: Baseline Factors Associated With No DRSS Score Improvement and ≥1-Step DRSS Improvement at Week 52



LOCF. The odds ratio was estimated using a logistic regression model and stepwise selection with baseline leakage area, baseline leakage distance to fovea, and lipid-lowering medication use at baseline control as the covariates. The model was decided by stepwise selection.

Proportion of Patients in the Sham Group by DRSS Response at Week 100



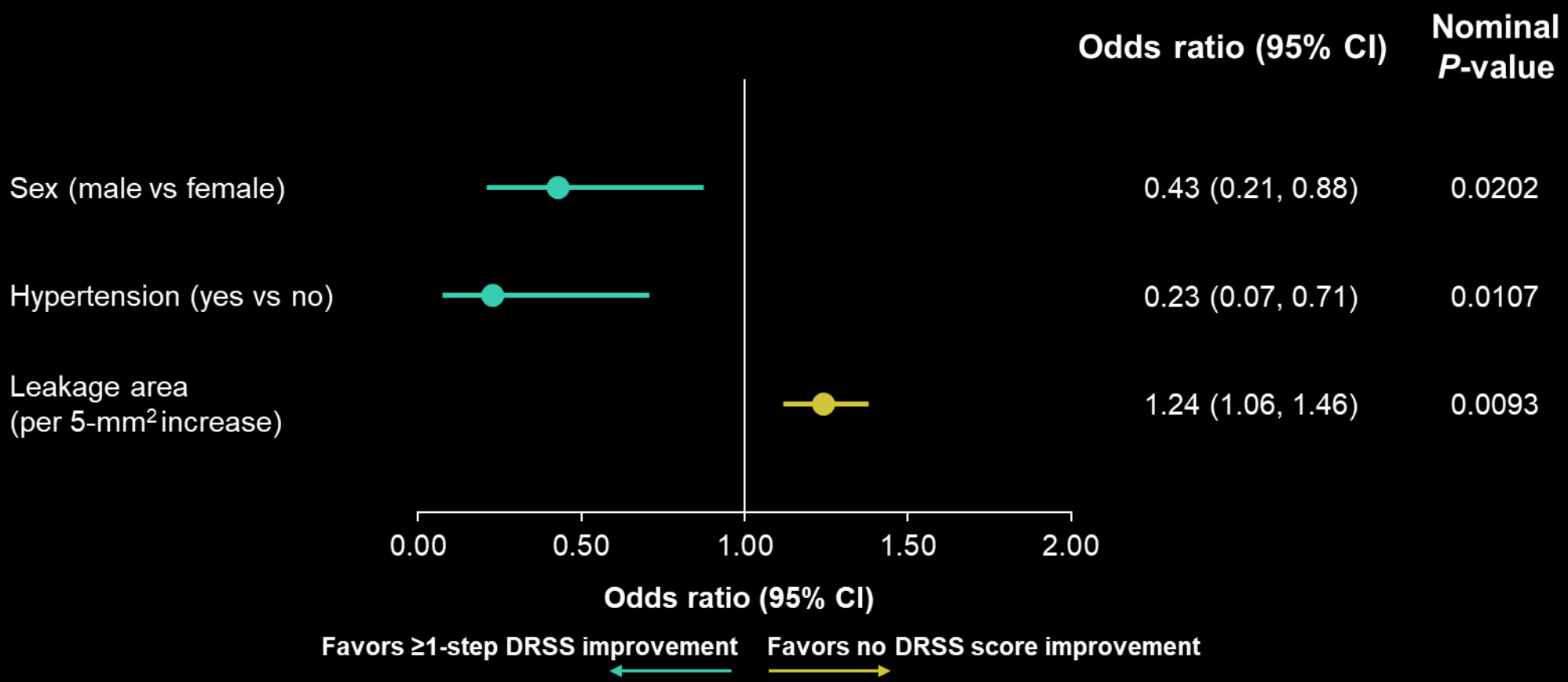
FAS, LOCF.

Baseline Characteristics by DRSS Response at Week 100 in Sham Patients

	Worsening or no change in DRSS (n=80)	≥1-step DRSS improvement (n=53)
Age, mean (SD), years	54.6 (10.9)	57.7 (9.2)
Female, n (%)	45 (56.3)	19 (35.8)
HbA1c, mean (SD), %	8.8 (1.6)	8.2 (1.5)
Type 2 diabetes, n (%)	73 (91.3)	50 (94.3)
Duration of diabetes, mean (SD), years	15.1 (8.4)	16.3 (10.7)
History of hypertension, n (%)	59 (73.8)	49 (92.5)
Lipid-lowering medication use, n (%)	50 (62.5)	39 (73.6)
ETDRS letter score, mean (SD)	82.7 (5.9)	82.8 (6.3)
DRSS score in study eye, n (%)		
47	57 (71.3)	42 (79.2)
53	23 (28.8)	11 (20.8)
CST, mean (SD), μm	253.3 (39.9)	243.5 (35.6)
Leakage area, mean (SD), mm^2	22.8 (11.9)	16.3 (11.2)
NP area, mean (SD), mm^2	0.4 (1.1)	0.2 (0.4)

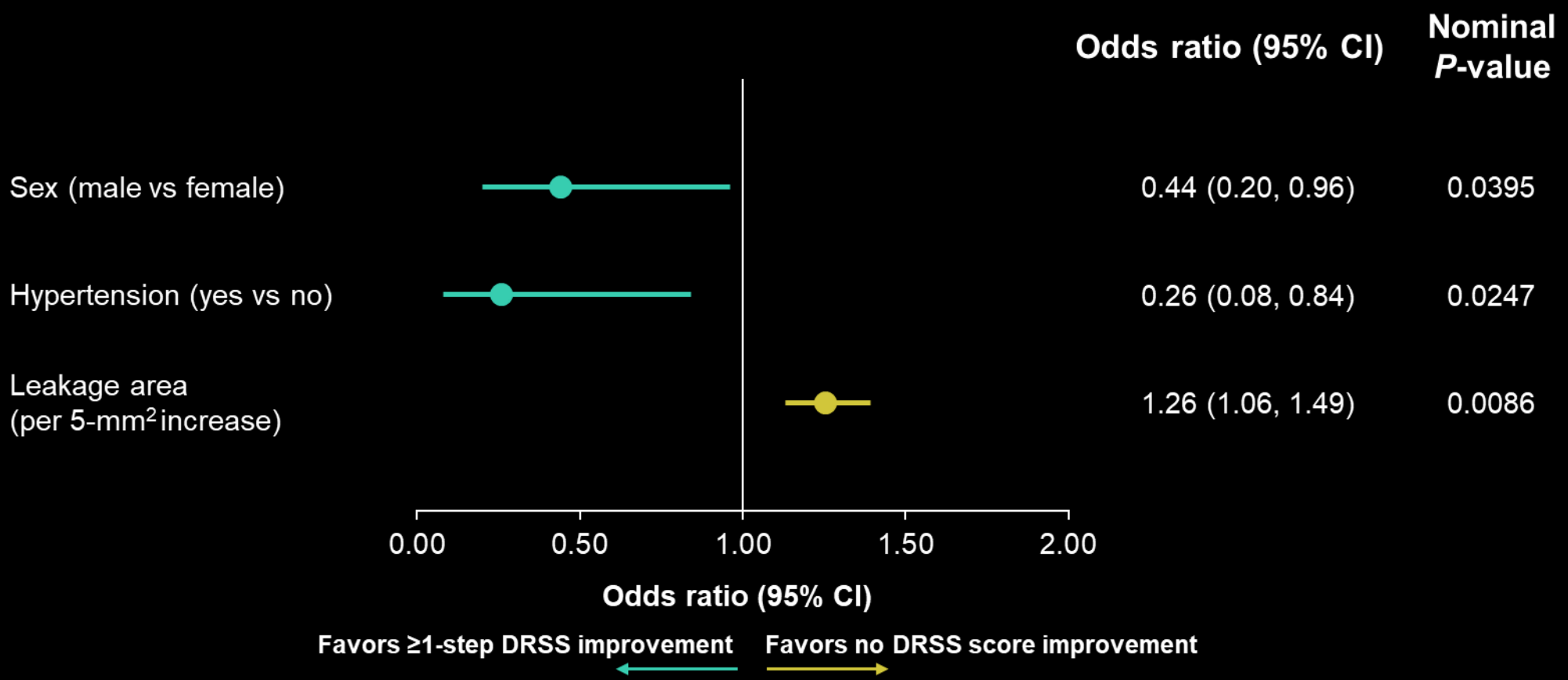
FAS, LOCF.

Univariate Analysis: Baseline Factors Associated With No DRSS Score Improvement and ≥1-Step DRSS Improvement at Week 100



LOCF. Inferential results were derived from a logistic regression model adjusted for randomization strata.

Multivariable Analysis: Baseline Factors Associated With No DRSS Score Improvement and ≥1-Step DRSS Improvement at Week 100



95.4% of patients with hypertension at baseline reported using antihypertensive medications

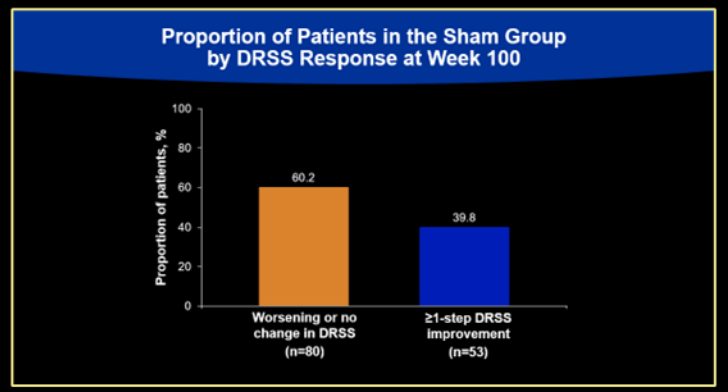
LOCF. The odds ratio was estimated using a logistic regression model and stepwise selection with sex, hypertension, and baseline leakage area as the covariates. The model was decided by stepwise selection.

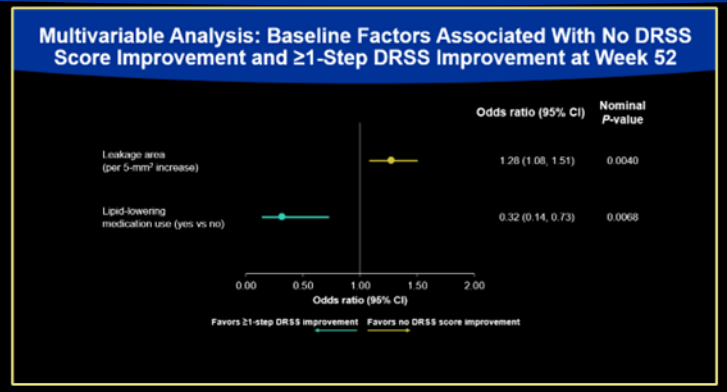
Limitations

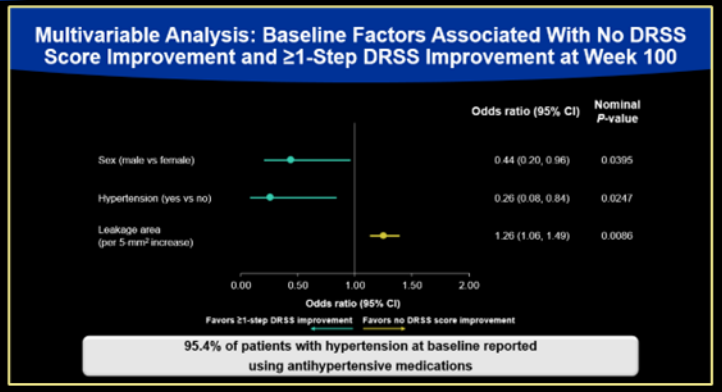
- The results may not be generalizable to a broader clinic patient population, as clinical trial participants may have more strict control of medical comorbidities
- Medication use (insulin and lipid control medications) was assessed at baseline only
- This was a post hoc exploratory approach
- The US FDA considers only a ≥2 step improvement or worsening in DRSS to be clinically relevant
  - For the purpose of this analysis, an improvement of ≥1 step in DRSS was considered; however, the clinical relevance of this is undetermined

US FDA, United States Food and Drug Administration.

Summary







- Over half of the patients (52.6%) in the sham group had no DRSS score improvement at Week 52, and this proportion increased to 60.2% at Week 100
- A larger baseline leakage area was the primary baseline factor that was associated with a higher risk of no DRSS score improvement at both Weeks 52 and 100
- Factors associated with improvement in DRSS score at Weeks 52 or 100 were use of lipid-lowering agents at baseline, being male, and having hypertension at baseline
  - Almost all patients with hypertension at baseline reported using antihypertensive medications, suggesting that hypertension control at baseline may be associated with improvement in DRSS score
- These findings can help inform physicians to prioritize patients who may require closer monitoring or earlier intervention