Vaginal/Vulvar Symptoms with Lasofoxifene Versus Fulvestrant in *ESR1*-Mutated, ER+/HER2- Metastatic Breast Cancer Patients

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Introduction

- Novel therapies with positive impacts on vaginal health are desirable for breast cancer patients since estrogen-depleting aromatase inhibitors (AIs) and degraders and modulators of the estrogen receptor (ER) are associated with symptoms of genitourinary syndrome of menopause (GSM)[1-3]
- Lasofoxifene (LAS), a next-generation endocrine therapy that acts as an ER antagonist at the breast, preliminarily prolonged median progression-free survival (PFS) compared with fulvestrant (Fulv; 6.04 vs 4.04 months; *P*=0.138) in metastatic breast cancer (mBC) patients with *ESR1* mutations (*mESR1*) who had progressed taking a prior AI and cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i), with a favorable safety profile, in the phase 2, ELAINE 1 study[4]
- As an estrogen agonist in urogenital tissues, LAS improved symptoms of vulvovaginal atrophy (VVA) in two phase 3 studies among postmenopausal women with moderate to severe VVA[5]
- The impact of LAS treatment on GSM symptoms in the mBC patient population of ELAINE 1 is unknown

Aim

- To investigate changes in vaginal/vulvar symptoms with LAS versus Fulv in women with ER+/HER2- mBC and acquired *mESR1* in the ELAINE 1 trial

Methods

- In the multinational (US, Canada, Israel), phase 2 ELAINE 1 study (NCT03781063), pre- or postmenopausal women with ER+/HER2- mBC and *mESR1* ctDNA whose disease progressed on prior AI-CDK4/6i treatment (duration ≥12 months) were randomized to receive oral LAS 5 mg (daily) or IM Fulv 500 mg (days 1, 15, and 29, then every 28 days) until disease progression/severe toxicity
- Efficacy measures were PFS (primary endpoint) and clinical benefit rate (CBR) at week 24
- Vaginal/vulvar symptoms were evaluated in an exploratory analysis using the vaginal (VAS) and vulvar (VuAS) assessment scales, instruments validated in breast cancer patients to assess dryness, soreness, irritation, and pain using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe)
  - English-speaking patients completed the VAS/VuAS at baseline and every 8 weeks until disease progression
  - Changes in the mean composite VAS/VuAS score (average of all reported scores for each symptom for a patient) and the mean score for the most bothersome symptom (the symptom with the greatest baseline score for a patient) over 16 weeks of treatment were analyzed for patients who had GSM symptoms at baseline

Results

Patient disposition and baseline characteristics

- Of 103 enrolled patients, 75% of LAS patients and 65% of Fulv patients completed the VAS/VuAS at baseline; among them, 23% and 30% had ≥1 moderate/severe symptom, respectively (Table 1)
- Women who completed the VAS/VuAS at baseline had a median age of 60 years in the LAS arm and 63 years in the Fulv arm (Table 1), with a mean baseline composite VAS/VuAS score of 0.21 and 0.38, respectively (Table 2)
- Most frequently reported most bothersome symptoms at baseline were vaginal dryness and vaginal pain

Table 1. Baseline characteristics

	Lasofoxifene	Fulvestrant
Total randomized, n	52	51
Completed the VAS/VuAS, n (%)	39 (75.0)	33 (64.7)
≥1 moderate/severe symptom*, n (%)	9 (23.1)	10 (30.3)
Age*, median (range), yrs	60 (37–84)	63 (38–82)
<50 yrs, n (%)	6 (15.4)	7 (21.2)
≥50 yrs, n (%)	33 (84.6)	26 (78.8)

*Characteristics in patients who completed the VAS/VuAS at baseline.
VAS, vaginal assessment scale; VuAS, vulvar assessment scale

Table 2. Composite VAS/VuAS scores and prevalence of symptoms

		Lasofoxifene (n = 39*)	Fulvestrant (n = 33*)
Composite VAS/VuAS score, Mean±SD		0.21±0.37	0.38±0.44
Symptoms present, n (%)			
VAS	Dryness	11 (28.2)	18 (54.5)
	Soreness	6 (15.4)	7 (21.2)
	Irritation	6 (15.4)	5 (15.2)
	Pain	7 (17.9)	9 (27.3)
VuAS	Dryness	6 (15.4)	12 (36.4)
	Soreness	5 (12.8)	5 (15.2)
	Irritation	5 (12.8)	8 (24.2)
	Pain	2 (5.1)	4 (12.1)

*Number of patients who completed the VAS/VuAS at baseline.
VAS, vaginal assessment scale; VuAS, vulvar assessment scale

Figure 1. Changes in VAS/VuAS scores in the overall population

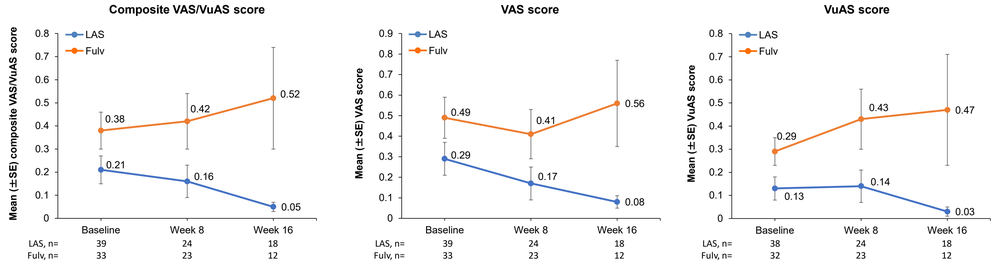
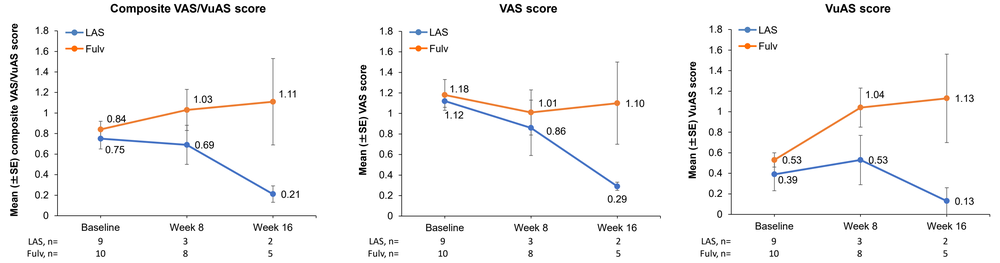


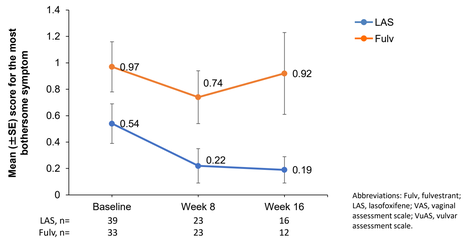
Figure 2. Changes in VAS/VuAS scores in patients with moderate/severe symptoms



Changes in VAS/VuAS scores

- Among patients who completed the VAS/VuAS at baseline, the mean composite VAS/VuAS score decreased (improved) from baseline to week 16 by 74% in LAS patients, but increased by 36% in Fulv patients (Figure 1)
- In the subgroup of patients with ≥1 moderate/severe symptom at baseline, mean composite VAS/VuAS score decreased from baseline to week 16 by 72% with lasofoxifene, in contrast to an increase by 32% with fulvestrant (Figure 2)
- The mean score for the most bothersome symptom decreased from baseline to week 16 by 65% with LAS versus 5% with Fulv (Figure 3)

Figure 3. Changes in the score for the most bothersome symptom



Abbreviations: Fulv, fulvestrant; LAS, lasofoxifene; VAS, vaginal assessment scale; VuAS, vulvar assessment scale.

Key Takeaways

- LAS at 5 mg/day improved vaginal/vulvar symptoms while Fulv worsened them in patients with *ESR1*-mutated mBC
- LAS may provide additional benefits on GSM symptoms and sexual health if used to treat breast cancer

Conclusions

- LAS at 5 mg/day numerically improved vaginal/vulvar symptoms relative to Fulv in a small sample size of mBC patients that were unselected for GSM symptoms in the ELAINE 1 study
- Baseline prevalence of moderate/severe vaginal symptoms was 20–30%, which may be under-reported for this population compared with the prevalence of vaginal dryness (19%–88%) previously reported in postmenopausal breast cancer patients/survivors taking AIs[1-3,6-8]
  - This lower prevalence may be due to patients minimizing symptoms less important than mBC disease control or being embarrassed to communicate sexual concerns to their oncologists
- Although limited by the open-label nature of the study and some imbalances between the treatment arms in baseline prevalence/severity of VVA symptoms, our exploratory analysis shows that LAS at 5 mg/day may potentially provide clinical benefits on GSM symptoms and sexual health when treating mBC
- Sexual and vaginal health with LAS plus abemaciclib will be assessed in the upcoming phase 3, Elaine 3 study in mBC patients using the FACT B-ES questionnaire, and further studies in early breast cancer patients with urogenital atrophy have been planned

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Disclosures

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