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Pharmacokinetics (PK) of Lasofoxifene (LAS) Monotherapy and Combined with Abemaciclib (Abema)

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Introduction

- Lasofoxifene (LAS), a next-generation selective estrogen receptor (ER) modulator (SERM) and potent, breast ER antagonist, was shown to:
  - Reduce fracture risk in postmenopausal women with osteoporosis[1]
  - Improve vaginal atrophy in postmenopausal women[2]
  - Exhibit antitumor activity in phase 2 studies of women with (ER+)/HER2-, *ESR1*-mutated, metastatic breast cancer (mBC) that progressed on endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitors (CDK4/6is)[3,4]
    - In the ELAINE 1 study, LAS alone prolonged progression-free survival (PFS) vs. fulvestrant (median ~5.6 vs 3.7 mos; *P*=0.138)[3]
    - In the ELAINE 2 study, LAS plus abemaciclib (Abema) was associated with a median PFS of ~13 months[4]
- Linear pharmacokinetics (PK) were seen with oral LAS following single (up to 100 mg) and multiple doses (up to 20 mg QD for 14d) in healthy volunteers; no clinically significant age or race differences were found[5,6]
  - LAS PK profiles between Caucasian and Japanese patients were similar[7,8]
- Here, we report select PK data of oral LAS (5 mg/day) from women with mBC and an *ESR1* mutation in the phase 2, ELAINE 1 and 2 studies

Objectives

To examine PK data of LAS 5 mg/day and investigate a possible drug-drug interaction between LAS and Abema

Methods

- Women with *ESR1*-mutated, ER+/HER2- mBC that progressed on endocrine therapy (ET) and CDK4/6 received oral LAS 5 mg/day as monotherapy (ELAINE 1) or combined with Abema (provided by Eli Lilly and Co) 150 mg BID (ELAINE 2)
- Blood was collected prior to daily dosing at baseline and weeks 2, 4, 8, and then every 4 weeks up to the final visit in ELAINE 1, and at baseline, weeks 2, 4, 6, and 8 in ELAINE 2
- LAS was assayed using validated high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS; linear range, 0.025 to 25.0 ng/mL); values below the lower limit of quantification (LLOQ) were reported as 0 ng/mL
- Abema and its 2 major, active metabolites (M2 and M20) were measured by validated Turbo Ion Spray LC/MS/MS (linear range, 1.00 to 500 ng/mL); values below the LLOQ were reported as <LLOQ ng/mL
- Mean plasma steady-state minimum concentrations (C_{min}) at each visit were calculated for LAS (ELAINE 1 and 2), and Abema and its M2 and M20 metabolites (ELAINE 2)
- LAS levels from ELAINE 1 and 2 were directly compared, while Abema, M2 and M20 plasma levels in ELAINE 2 were compared with previously reported levels; the relationship of LAS concentrations with PFS was also explored

Results

Figure 1. Plasma concentrations of lasofoxifene over time in (A) ELAINE 1 and (B) ELAINE 2

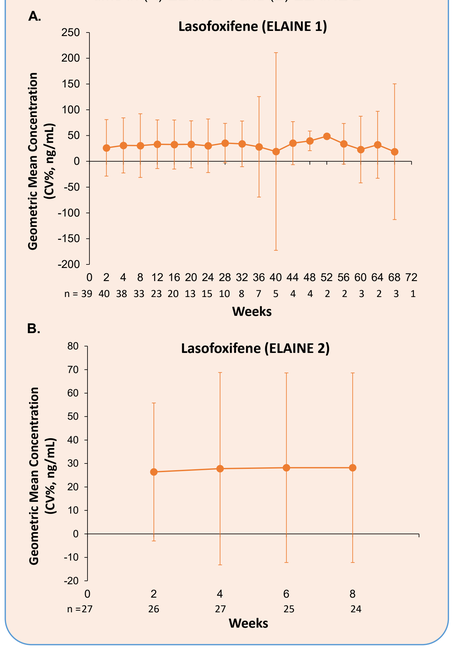
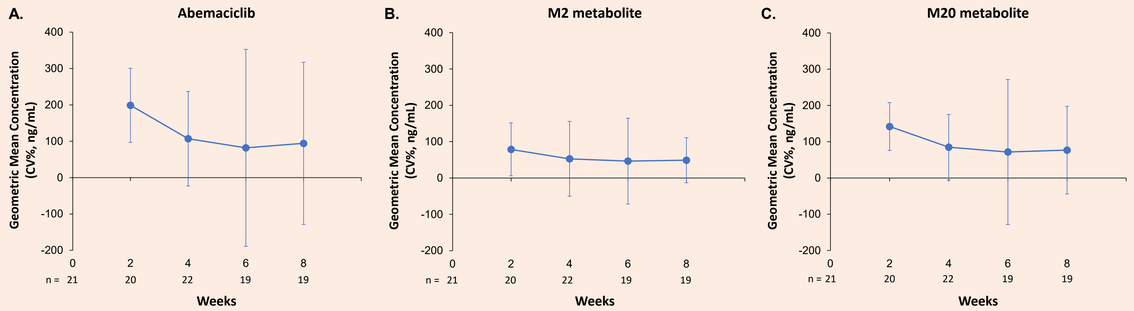


Table 1. Steady-state minimum concentrations (C_{min} [CV%]) for abemaciclib and M2 and M20 metabolites reported in the EMA EPAR[9] and in ELAINE 2

	C_{min} (CV%), ng/mL		
	Abemaciclib	**M2**	**M20**
European Medicines Agency[a]	143 (110)	62.6 (67)	113 (58)
ELAINE 2[b]	113.8 (179.3)	55.6 (91.5)	90.7 (119.7)

[a]European Medicines Agency Review of Pharmacokinetics for Abemaciclib (Verzenios). [b]Subjects having no abemaciclib dose reduction; 4 subjects had a dose reduction. C_{min}, steady-state minimum concentration; CV, coefficient of variation; EMA, European medicine agency; EPAR, European public assessment report.

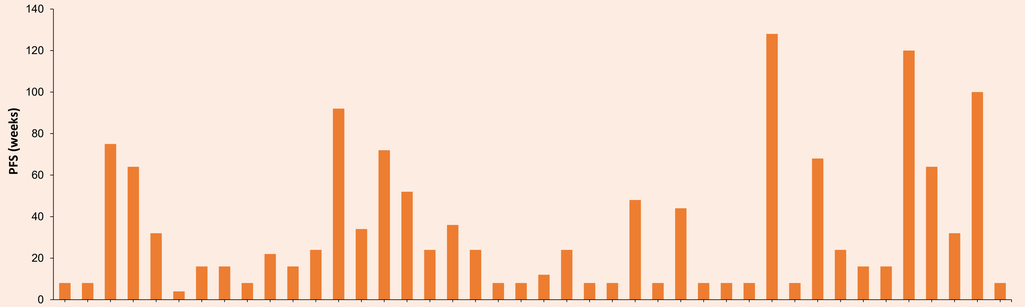
Figure 2. Plasma concentrations of (A) abemaciclib, (B) M2 metabolite, and (C) M20 metabolite over time in ELAINE 2



Data from patients who received oral LAS (5 mg/day) plus Abema (150 mg BID).

- Levels of LAS were similar between the ELAINE 1 and 2 studies and were consistent across visits with no evidence of longer-term or unexpected accumulation (**Figure 1**); across all time points for subjects who had PK samples assessed, the geometric mean C_{min} of LAS was 30.4 ng/mL (CV%, 56.9) in ELAINE 1 and 27.9 ng/mL (CV%, 36.1) in ELAINE 2
- Inter-subject variability was observed in plasma Abema concentrations in ELAINE 2; the mean concentrations of Abema and its M2 and M20 metabolites were comparable across all timepoints assessed among patients who did not have Abema dose reductions (**Figure 2**)
- The mean C_{min} for abemaciclib, M2 and M20 are similar to the C_{min} previously reported in the European public assessment report for Abema[9] (**Table 1**)
- Length of PFS was not related to LAS in the ELAINE 1 trial (shown descriptively in **Figure 3**) or LAS or Abema levels in the ELAINE 2 trial

Figure 3. Mean C_{min} of lasofoxifene across visits for each subject and PFS in ELAINE 1



PFS, progression-free survival. Mean concentrations for LAS and Abema were calculated for each individual based on values obtained across patient visits.

Key Takeaways

- PK data for LAS 5 mg/day were consistent with previous clinical trials, resulting in similar steady-state concentrations in patients across several studies
- Addition of Abema to LAS did not appear to alter the PK of LAS in ELAINE 2 compared with monotherapy in ELAINE 1, suggesting little to no drug-drug interaction
- Abema concentrations in ELAINE 2 were consistent with previous monotherapy data, suggesting no impact of LAS on Abema PK

Conclusions

- The C_{min} for LAS from both ELAINE studies was consistent with that predicted for 5 mg/day LAS from the non-oncologic program (26 ng/mL) and an ethno-bridging study (Japanese subjects: 30 ng/mL, Caucasians: 33 ng/mL),[6] suggesting no significant effect of Abema on the PK of LAS
- Abema PK data from ELAINE 2 were consistent with published data;[9] little to no interactions between LAS and the metabolism of Abema or its M2 and M20 metabolites were observed
  - This is not unexpected, as lasofoxifene does not have a significant inhibitory or induction effect on CYP3A4,[6] the major metabolic pathway of abemaciclib[10]
- These results support the continued development of LAS alone and combined with Abema for treating ER+/HER2-, *ESR1*-mutated mBC that progressed on ET and CDK4/6is

References

1. Cummings SR, et al. *N Engl J Med*. 2010;362:686-696. **2.** Portman DJ, et al. *Menopause*. 2015;22:1385-1386. **3.** Goetz MP, et al. *Ann Oncol*. 2023;In Press. **4.** Damodaran S, et al. *Ann Oncol*. 2023;In Press. **5.** Gardner M, et al. *J Clin Pharmacol*. 2006;46:52-58. **6.** Data on file. Sermonix Pharmaceuticals. **7.** Fountaine RJ, et al. *J Clin Pharmacol*. 2006;46:693-699. **8.** Jhee S, et al. 12th AACR-JCA Joint Conference: Breakthroughs in Cancer Research. 2022:Abstract A83. **9.** Assessment report: Verzenios (International non-proprietary name: abemaciclib). European Medicines Agency. Procedure No. EMEA/H/C/004302/II/0013. 2022. **10.** Verzenios (abemaciclib) 50, 100, 150 mg film-coated tablets Summary of Product Characteristics. Eli Lilly and Company. Indianapolis, IN.

Disclosures

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