An Open-label, Randomized, Multi-center Phase 2 Study Evaluating the Activity of Lasofoxifene Relative to Fulvestrant for the Treatment of Postmenopausal Women with Locally Advanced or Metastatic ER+/HER2- Breast Cancer with an ESR1 Mutation

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INTRODUCTION
One cause of endocrine resistance in the presence of activating ESR1 mutations within breast cancer cells, which from preclinical studies demonstrate constitutive, ligand–independent estrogen receptor (ER) activation. Because of the relative endocrine resistance of these mutations to approved hormonal agents, there is a significant unmet medical need for the investigation of new targeted endocrine therapies that have potenti activity in the presence of ESR1 mutations.

SERM’s initiated a Phase 2 clinical trial in postmenopausal women with ER+/HER2- breast cancer who progressed on an aromatase inhibitor (AI) in the adjuvant setting and who have an ESR1 mutation. The clinical trial will evaluate investigational lasofoxifene, a potent selective estrogen receptor modulator (SERM).

LASOFOXIFENE
• Lasofoxifene has been shown to inhibit tumor proliferation within in vitro and in vivo breast cancer animal models.
• In vivo mice studies have also demonstrated dose dependent efficacy in ESR1 mutated breast cancer cells as well as a reduction in metastasis when compared to fulvestrant.
• In humans, lasofoxifene has excellent oral bioavailability and volume of distribution, and is 99% bound in plasma.
• The drug has been well tolerated with oral doses as high as 10 mg given once a day (mg/d).
• In a large five-year osteoporosis trial, an 83% reduction in vertebral fractures was observed in patients taking 5 mg/day of lasofoxifene compared to placebo.

Lasofoxifene binding causes an "OFF" state in ER mutated proteins. WT unbound, WT bound, ER mutated, & ER mutated bound to lasofoxifene.

REFERENCES
1. Paul V. Plourde MD, Lee S. Schwartzberg MD, Geoffrey L. Greene PhD, David J Portman MD, Barry S Koom PhD, Simon N Jenkins PhD, Ping-Yu Liu PhD, Miriam D Portman MD and Matthew P Goetz MD

CONCLUSIONS
• Lasofoxifene has a well-characterized safety profile from Phase 1–3 studies in over 10,000 women in non-oncology indications.
• Lasofoxifene significantly reduced the incidence of ER+ breast cancer by 83% in a large five-year osteoporosis study.
• In non-clinical models of breast cancer, lasofoxifene demonstrated superior efficacy to fulvestrant in inhibiting tumor growth and metastases to liver and lung, particularly in ESR1 mutant tumors.
• Non-clinical findings may be explained by lasofoxifene’s binding affinity to mutated estrogen receptors and its favorable PK characteristics.
• These aspects, coupled with lasofoxifene- specific conformational changes to the receptor, effectively block estrogen mediated proliferation.
• These data clearly support further investigation of this molecule in a clinical setting.
• This trial will be the first prospective controlled randomized study investigating a SERM for the targeted treatment of ER+ advanced breast cancers with an ESR1 mutation.
• If successful, lasofoxifene will confer a major benefit to women with metastatic breast cancer and thereby delay the need for toxic chemotherapy.

Study centers are now being considered and trial to be initiated in January 2019.

Investigators interested in participating should contact our CRO partner Lincal-Accelovance, Laura Smeral, lsmoral@linclal.accelovance.com.

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VISIT SCHEDULE
• Vital signs, height, weight, physical exam, and ADV (adverse events) assessment at each visit
• Blood every two weeks; one blood sample drawn at each visit
• MRI or CT of the chest, abdomen and pelvis every two months or sooner if clinically indicated
• CBC with differential, routine chemistries, and sample for PK analysis every visit

STATISTICAL PLAN
PFS will be compared between the lasofoxifene and fulvestrant groups. The primary outcome measure will be the Kaplan-Meier survival estimate of PFS and logrank test will be used to compare the Kaplan-Meier survival curves.

Baseline patient characteristics will be compared between the following groups:
1. ESR1 mutation positive
2. ESR1 mutation negative

The PFS will be estimated using the Kaplan-Meier method and the lasofoxifene over fulvestrant hazard ratio will be estimated by the Cox proportional hazards model.

TREATMENT
• Open label, randomized, multicenter study
• Screening within thirty days of enrollment
• Subjects treated until documented disease progression or death
• Full recruitment into study estimated to occur within twelve to fifteen months, with another twelve months of follow up before the primary outcome measure is analyzed

STUDY DESIGN
• Postmenopausal women with:
  1. ER+/HER2- advanced breast cancer with either measurable or non-measurable disease
  2. ECOG performance status of 0 or 1
  3. History of a positive human chorionic gonadotropin (hCG) study
  4. Radiotherapy within 30 days prior to enrollment
  5. History of long QT syndrome or a QT interval greater than 500 ms
  6. History of a pulmonary embolus (PE) or deep vein thrombosis (DVT)
  7. History of a positive human papillomavirus (HPV) test
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EXCLUSION CRITERIA
Subjects who meet any of the following criteria will be excluded from entering the trial:
1. Known allergy or sensitivity to lasofoxifene
2. Presence of brain metastasis or carcinomatosis involving the lung
3. Impending visceral crisis as assessed by the investigator within 30 days prior to randomization
4. History of a pulmonary embolus (PE) or deep vein thrombosis (DVT) within the last 2 years
5. Known drug or alcohol abuse
6. Known uncontrolled diabetes mellitus (e.g., requiring insulin or oral glucose lowering agents)
7. Condition, disease, syndrome or a QT interval greater than 500 ms
8. History of a positive human chorionic gonadotropin (hCG) study

A comparison between the lasofoxifene and fulvestrant groups for each efficacy outcome will be assessed with the Kaplan-Meier survival analysis.

EVENTS
• A planning event will be held to finalize the study protocol.
• The protocol will be reviewed by our Data Safety and Monitoring Board (DSMB).
• Investigators will be kept informed of the study results.

DECISION MAKING
• Investigators will have the opportunity to discuss the study results with the DSMB.
• Investigators will be informed of any changes to the study protocol.
• Investigators will have the opportunity to provide feedback on the study results.

CONCLUSION
• Lasofoxifene is an ER+/HER2- breast cancer with an ESR1 mutation.
• Lasofoxifene significantly reduced the incidence of ER+ breast cancer by 83% in a large five-year osteoporosis study.
• Lasofoxifene demonstrated superior efficacy to fulvestrant in inhibiting tumor growth and metastases to liver and lung, particularly in ESR1 mutant tumors.
• Non-clinical findings may be explained by lasofoxifene’s binding affinity to mutated estrogen receptors and its favorable PK characteristics.
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