2 Synopsis

Sponsor: Merrimack Pharmaceuticals, Inc. One Kendall Square, Suite B7201, Cambridge, MA 02139, USA
Name of Finished Product: Seribantumab injection
Name of Active Ingredient: Seribantumab
Study Title: A Randomized, Double-Blind Phase 2 Trial of Exemestane +/- MM-121 in Postmenopausal Women with Locally Advanced or Metastatic Estrogen Receptor Positive (ER+) and/or Progesterone Receptor Positive (PR+), HER2 Negative Breast Cancer (NCT01151046)
Investigators: Lead Investigator: Michaela Higgins MD, Massachusetts General Hospital, 55 Fruit St. Boston, MA 02114
Study Centers: The study was performed at 44 study centers in the United States, Canada, Germany, Spain, and Russia
Publication (reference): Not applicable
Studied Period: 05 July 2010 (first patient enrolled) to 30 Aug 2013 (The data cutoff point at which 51 [44.3%] patients remained on study, including 27 [48.2%] patients who were receiving seribantumab plus exemestane and 24 [40.7%] patients who were receiving placebo plus exemestane.)
Study Phase: Phase 2
Objectives: **Primary:** To determine whether the combination of seribantumab plus exemestane is more effective than exemestane alone, based on progression free survival (PFS). **Secondary:** • To compare the efficacy of the combination of seribantumab plus exemestane to exemestane alone using overall survival (OS), objective response (OR) rate, duration of response (DOR), and clinical benefit rate (CBR) • To determine the safety profile of the seribantumab plus exemestane combination • To determine the pharmacokinetic (PK) parameters for seribantumab in the seribantumab plus exemestane combination within a subset of patients • To determine the immunogenicity parameters of seribantumab in the seribantumab plus exemestane combination **Exploratory:** • To explore the utility of an epidermal growth factor receptor (EGFR)-ligand and other biomarker profiles as predictors of response to seribantumab and/or exemestane in formalin-fixed tumor samples (FFTS) and serum samples • To compare change in number of circulating tumor cells (CTCs) following treatment

Methodology:
This was an international, multicenter, double-blind, randomized, placebo-controlled Phase 2 study of the efficacy, safety, PK, and immunogenicity of the combination of seribantumab plus exemestane (experimental arm) or placebo plus exemestane (control arm) in postmenopausal women with locally advanced or metastatic (ER+ and/or PR+, human epidermal growth factor 2 [HER2] negative) breast cancer. Patients were randomized to receive either experimental or control treatment at a 1:1 ratio, and randomization was stratified based on the following 2 factors:

- The setting in which patient's disease has progressed (patient progressed during or within 6 months of completion of adjuvant treatment with a non-steroidal aromatase inhibitor and/or tamoxifen vs. patient progressed following treatment with prior anti-estrogen therapy in the locally advanced or metastatic setting).
- Presence of bone-only metastatic disease (yes vs. no). Patients with no measurable disease and at least 2 bone lesions will be considered "bone-only" for the purposes of the study analysis.

The study was monitored by a Data Monitoring Committee. One formal, prespecified interim analysis was performed to determine if the trial should be stopped for futility.

Number of Patients:
Planned: 130
Randomized: 118
Treated: 115
Analyzed: 115

Diagnosis and Main Criteria for Inclusion:

- Progression of locally advanced or metastatic disease after treatment with prior anti-estrogen therapy or progression during treatment with or within 6 months of discontinuation of an adjuvant non-steroidal aromatase inhibitor and/or tamoxifen
- Histologically or cytologically confirmed ER+ and/or PR+ and HER2 negative breast cancer
- Documented locally advanced or metastatic disease with at least 1 radiologically measurable lesion as defined by response evaluation criteria in solid tumors (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) except for patients with bone-only metastatic disease with at least 2 lesions on a bone scan or other imaging modality such as x-ray, computed tomography (CT), positron emission tomography CT, or magnetic resonance imaging and disease progression on prior therapy, based on the appearance of new lesions
- Postmenopausal, female patients defined by > 5 years since onset of menopause and luteinizing hormone/follicle-stimulating hormone levels in the postmenopausal range in women whose menopause occurred < 5 years before inclusion
- Unstained tumor tissue available for analysis
- Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2
- Adequate bone marrow reserves as evidenced by absolute neutrophil counts (ANCs) > 1500/µl without the use of hematopoietic growth factors, platelet count > 100,000/µl, and hemoglobin > 9 g/dL
- Adequate hepatic function as evidenced by serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN; $\leq 5 \times$ ULN was acceptable if liver metastases were present, and $\leq 5 \times$ ULN of ALP was acceptable if bone metastases were present
- Adequate renal function as evidenced by a serum creatinine $\leq 1.5 \times$ ULN
- Recovered from clinically significant effects of any prior surgery, radiotherapy, or other antineoplastic therapy. Patients with a known peripheral neuropathy had to be Grade 1 or less, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0
- $\geq$ 18 years of age

Test Product, Dose and Mode of Administration, Lot Numbers:

Test Product:

Seribantumab or placebo. Seribantumab or placebo were supplied and labeled for investigational use in a blinded manner:

- Seribantumab formulation: clear liquid supplied in sterile, single-use vials containing 10.1 mL of seribantumab at a concentration of 25 mg/mL in 20 mM histidine, 150 mM sodium chloride, pH 6.5.
- Placebo formulation: clear liquid of histidine solution supplied in sterile, single-use vials containing a solution of 20 mM histidine, 150 mM sodium chloride, pH 6.5, about 300 mOsm/kg, labeled in an equivalent manner as seribantumab to maintain the study blind.

Dose and mode of administration:

Seribantumab (or matching placebo) 40 mg/kg loading dose and 20 mg/kg weekly administered as an intravenous infusion.

Lot Numbers:

Seribantumab: 1-FIN-1098, 1-FIN-1607, 1-FIN-1370, 1-FIN-1315, 1-FIN-1288, 1-FIN-1607

Placebo: 373-03-001

Duration of Treatment: Patients were treated until disease progression, death, or intolerable toxicity.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Reference Therapy:

Exemestane supplied as commercially available white film-coated tablets containing 25 mg exemestane for oral administration.

Dose and Mode of Administration:

Patients received exemestane 25 mg by mouth once daily after a meal. Patients self-administered exemestane at their homes.

Lot Numbers:

Not applicable. Commercially available exemestane was provided to patients by the Sponsor.

Criteria for Evaluation

Efficacy:

The analysis of PFS (the primary efficacy endpoint) was performed on the Safety population and repeated using the intent-to-treat (ITT) population (which included all randomized patients) as a sensitivity measure. The tumor assessment related to the efficacy endpoints (PFS and OR) was performed using RECIST v1.1 based on investigator assessment. Progression free survival is defined as the number of weeks from the date of randomization to the date of death or progression. If a patient did not experience death or progression during the study, that patient's PFS data were censored as of the last valid tumor assessment, unless the patient discontinued due to symptomatic deterioration. If deterioration occurred, the subject was counted as having a progressive disease (PD) event at the time of treatment termination. If a patient discontinued due to symptomatic deterioration and was subsequently evaluated for a PD response, for which PD was determined, then the time to PD was reset from the time to symptomatic deterioration to the time PD subsequently was evaluated, even if the documented PD occurred after treatment discontinuation. PFS was compared between arms using a log-rank test stratified by the following factors:

- The setting in which patient's disease progressed (patient progressed during or within 6 months of completion of adjuvant treatment with a non-steroidal aromatase inhibitor and/or tamoxifen vs. patient progressed following treatment with prior anti-estrogen therapy in the locally advanced or metastatic setting); and
- Presence of bone-only metastatic disease (yes vs. no). Patients with no measurable disease and at least 2 bone lesions were considered "bone-only" for the purposes of the study analysis.

Analyses were based on the actual strata into which the patient should have been classified at the time of randomization. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were estimated using a stratified Cox proportional hazard model. An additive Cox proportional hazards model with both stratification factors in combination with the treatment effect was also used to estimate the HR. The results for this model are not presented. Secondary efficacy analyses of OS, OR rate, DOR, and CBR were also performed.

Biomarker Analysis:

Biomarker analyses were performed to evaluate the utility of an EGFR-ligand and other biomarkers as predictors of response to seribantumab plus exemestane in FFTS. Only patients with non-missing biomarker results were used in the analysis.

Safety:

Safety assessments included adverse events (AEs), treatment-emergent adverse event (TEAEs), TEAEs related to study treatment, TEAEs Grade ≥ 3, serious TEAEs, TEAEs leading to discontinuation, deaths, clinical laboratory evaluations (including hematology, serum chemistry, coagulation, urinalysis, vital signs, electrocardiogram, multi-gated acquisition or echocardiogram, ECOG performance status, and physical examinations). Adverse events were graded according to NCI CTCAE v4.0.

Bioanalytical Methods:

Biomarkers:

Biomarkers were measured in formalin-fixed, paraffin-embedded tissue sections using fluorescence-based quantitative immunohistochemistry (Fl-qIHC), chromogenic-based ribonucleic acid-*in situ* hybridization (RNA-ISH), and quantitative reverse transcription polymerase chain reaction (RT-PCR). Members of the EGFR family, including the EGFR, HER2, and ErbB3 (HER3) receptors, were planned to be analyzed using Fl-qIHC and RT-PCR. The betacellulin (BTC) and heregulin (HRG) ligands were planned to be analyzed by RNA-ISH and RT-PCR.

Pharmacokinetics: Seribantumab concentrations in blood samples were measured by a central analytical laboratory using an enzyme-linked immunoassay (ELISA) for seribantumab.

Immunogenicity:

Anti-seribantumab antibodies were measured in blood samples using an ELISA.

Statistical Methods:

Sample Size Determination

The sample size determination was based on the assumption that the median PFS time would be 4 months in the control arm. A total of 78 PFS events were needed to detect a 50% reduction in the HR of 0.5 in the experimental arm relative to the control arm with 85% power using a log-rank test at an overall 1-sided 0.025 level. The calculation took into account an interim analysis of PFS for futility based on a gamma (–3) spending function in EAST® software. Based on an anticipated accrual period of 18 months followed by a 4-month follow-up after the randomization of the last patient, it was determined that 130 patients (65 in each arm) would be necessary to achieve the targeted number of 78 confirmed progression events.

Efficacy:

The PFS curves were plotted using Kaplan-Meier estimates. The primary analysis of PFS was undertaken using a stratified log-rank test incorporating the 2 stratification factors into which the patient was classified at the time of randomization (actual strata). Statistical testing compared the treatment arms for overall PFS using a 2-sided significance level set at $\alpha = 0.05$. The analysis of the primary endpoint was performed on the Safety population (a subset of the ITT population who received at least 1 dose of study treatment), and a sensitivity analysis of the primary endpoint was performed on the ITT population. This change in the planned analysis from the statistical analysis plan reflected the observation that, from a clinical perspective, the most meaningful results in this Phase 2 trial would be on patients who were randomized and received study treatment. Patients who were randomized and then discontinued before being treated were censored at randomization based on the data handling rules for PFS. These patients did not provide additional information to the primary analysis. This decision was implemented prior to the trial being unblinded. The final analysis was triggered once 78 PFS confirmed events had occurred. A data cutoff date for this final analysis was established as of 30 Aug 2013. As of this date, there were a total of 84 PFS events. A stratified Cox proportional hazards model was constructed to estimate the HR and corresponding 95% CI of the experimental arm relative to the control arm.

Safety:

Analyses of safety parameters and clinical laboratory endpoints were performed on the Safety population. The primary analysis of safety was based on TEAEs summarized with respect to the type, frequency, severity, seriousness, and relatedness. Immunogenicity data were captured and analyzed using an electrochemiluminescence reader, and statistical analyses included descriptive statistics such as arithmetic group means, standard deviation, percent (%) difference, and coefficient of variation (CV).

Biomarkers:

The biomarker population was analyzed retrospectively and was defined as a subset of the Safety population, which included all patients with non-missing HRG quantitative RT-PCR data. Biomarker-positive (BM+) and biomarker-negative (BM–) groups were defined as a HRG $-\Delta Ct$ score of ≥ -5 and ≤ -5, respectively. All efficacy analyses of the BM subgroups were performed using an unstratified Cox proportional hazard model. Members of the EGFR family, including the EGFR, HER2, and ErbB3 (HER3) receptors, were planned to be analyzed using Fl-qIHC and RT-PCR. The BTC and HRG ligands were planned to be analyzed by RNA-ISH and RT-PCR.

Pharmacokinetics: PK parameters derived from whole blood samples were reported for the first 30 patients enrolled and were summarized by visit with the following statistics: number of evaluable patients (N), geometric mean, CV relative to the geometric mean, and 95% CI relative to the geometric mean.

Estimation of PK parameters was performed using standard non-compartmental methods. Compartmental methods were not undertaken.

Summary of Results:

A total of 118 patients were enrolled (the ITT population), 3 of whom discontinued before receiving study treatment. The remaining 115 patients who received at least 1 dose of study treatment constituted the Safety population, with 56 patients in the experimental arm and 59 patients in the control arm. Patients in both arms were similar in terms of demographics and disease history.

A total of 82 (71.3%) patients discontinued treatment due to PD: 37 (66.1%) patients in the experimental arm and 45 (76.3%) patients in the control arm. As of the data cutoff point of 30 Aug 2013, 45 (80.4%) patients in the experimental arm and 41 (69.5%) patients in the control arm were censored from the primary efficacy and safety analyses. The primary reason for censoring was that the patient was alive at the data cutoff point for 45 (80.4%) patients in the experimental arm and 41 (69.5%) patients in the control arm. Of these, 21 patients were subsequently included in the biomarker analysis which was conducted at a later date.

Efficacy:

- *Progression Free Survival*: Overall PFS (the primary endpoint) in the Safety population was observed in 37 (66.1%) patients in the experimental arm compared to 45 (76.3%) patients in the control arm. The estimated median PFS was 15.9 weeks for patients in the experimental arm and 10.7 weeks for patients in the control arm. The difference in PFS between arms was not statistically significant (HR = 0.772 [p = 0.2486]).
- *Overall Survival:* Eleven (19.6%) patients in the experimental arm and 18 (30.5%) patients in the control arm died. Median OS was not evaluable in the seribantumab arm because most patients (45/56 [80.4%]) were censored because they were alive at the time of database lock. The estimated median OS was 96.3 weeks for patients in the control arm with a 95% CI (51.4-96.3). There was a strong trend in OS in favor of seribantumab with a HR of 0.408 and a nominal p-value of 0.0342.
- *Objective Response Rate:* An OR (complete response or PR) was achieved in 4 (7.1%) patients in the experimental arm and 4 (6.8%) patients in the control arm. Two (3.6%) patients in the experimental arm and 2 (3.4%) patients in the control arm who had metastatic disease without bone lesions achieved an OR. Similar results were seen in the adjuvant setting without bone lesions, with 2 (3.6%) patients in the experimental arm and 2 (3.4%) patients in the control arm achieving an OR.
- *Duration of Response:* The median DOR was not reached in either arm.

Biomarkers: In the experimental arm, 39 (70%), 27 (48%), and 46 (82%) patients, respectively, had evaluable biomarker results using RT-PCR, RNA-ISH, and quantitative immunohistochemistry; in the control arm, 37 (63%), 28 (47%), and 43 (73%) patients had biomarker results for the same measures. Among the total of 115 patients, 76 (66%) patients were included in the BM population. The HR for PFS of the BM population was 0.74 (95% CI [0.45-1.24]). Of the 76 patients in the BM population, 34 (45%) patients were BM+, and 42 (55%) patients were BM–, as defined by their HRG messenger ribonucleic acid (mRNA) expression levels measured by RT-PCR. In the control arm, patients with low HRG mRNA levels had a longer median PFS of 5.36 months compared to a median PFS of 1.85 months in patients with high HRG mRNA levels. The difference was statistically significant (p = 0.004) with a HR of 3.4 (95% CI [1.48-7.85]). Patients in the control arm with high HRG mRNA levels had a shorter median PFS of 1.85 months compared to patients in the experimental arm with a PFS of 3.82 months. There was a strong trend in PFS in favor of seribantumab with a HR of 0.26 (95% CI [0.11-0.63]) and a nominal p-value of 0.039.

Safety:

In the Safety population, median duration of exposure was 107 days for the experimental arm and 71 days in the control arm. In the experimental arm, 37 (66.1%) patients received 75% of the planned doses in Cycles 1 and 2 compared to 42 (71.2%) patients in the control arm.

Safety Findings

Table: Overall Safety Results

	Seribantumab plus Exemestane N = 56 n (%)	**Placebo plus Exemestane N = 59 n (%)**
Patients with ≥ 1 AE	48 (85.7%)	51 (86.4%)
Patients with ≥ 1 TEAE	48 (85.7%)	50 (84.7%)
TEAEs ≥ Grade 3	14 (25.0%)	15 (25.4%)
TEAEs related to study treatment	40 (71.4%)	32 (54.2%)
Serious TEAEs	7 (12.5%)	11 (18.6%)
TEAEs leading to death[a]	2 (3.6%)	1 (1.7%)
TEAEs leading to dose discontinuation	2 (3.6%)	0

[a] All fatal events were assessed as not related to study treatment.
Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event

Treatment-Emergent Adverse Events

The most frequently reported TEAEs in the experimental arm overall were diarrhea, nausea, fatigue, and arthralgia. A summary of TEAEs, by grade, regardless of relationship to study treatment, is provided below.

Table: Summary of TEAEs by Grade Regardless of Relationship to Study Treatment

Grade	**Seribantumab plus Exemestane N = 56 n (%)**	**Placebo plus Exemestane N = 59 n (%)**
1	11 (19.6%)	17 (28.8%)
2	23 (41.1%)	18 (30.5%)
3	12 (21.4%)	11 (18.6%)
4	0 (0.0%)	3 (5.1%)
5	2 (3.6%)	1 (1.7%)

The most frequently reported TEAEs considered to be related to study treatment in the experimental arm were diarrhea, fatigue, nausea, mucosal inflammation, and dysgeusia. No Grade 4 or Grade 5 TEAEs considered to be related to study treatment were reported in either arm.

Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

Deaths were reported for 2 (3.6%) patients in the experimental arm (due to PD and cardiovascular insufficiency due to hepatic failure) and 1 (1.7%) patient in the control arm (due to PD). All deaths were considered to be unrelated to study treatment.

Immunogenicity:

One patient in the experimental arm and 6 patients in the control arm tested positive for the presence of anti-seribantumab antibodies. One experimental arm patient and 1 control arm patient had pre-treatment positive samples suggesting pre-existing antibodies. Two control arm patients had single borderline positive post-dose samples. Three control arm subjects had pre-treatment negatives and at least 1 post-dose positive sample. However, 1 patient's antibody levels increased substantially over the treatment period for an unknown reason. There is no clear reason for these 3 control-arm anomalous results.

Pharmacokinetics:

All seribantumab PK parameters, including C_{max}, C_{last}, AUC_{last}, and $t_{last,}$ increased over time with increasing exposure, whereas t_{max}, decreased during the same time period. Seribantumab steady state

appeared to have been reached between C4 and C5; however, insufficient samples from subsequent cycles were available to accurately determine whether steady-state pre-treatment concentrations increased beyond these cycles.

Conclusions:

The study enrolled a heterogeneous population of postmenopausal women with locally advanced or metastatic ER+ and/or PR+, HER2 negative breast cancer.

Efficacy

The addition of seribantumab to exemestane did not produce a statistically significant prolongation of PFS (the primary endpoint), although the HR appeared to favor the seribantumab arm (HR = 0.772; 95% CI [0.496-1.201]); thus, the primary endpoint of the study was not met (p = 0.2486). Overall survival results trended in the same direction as PFS (HR = 0.408; 95% CI [0.186-0.894]), however 18 (32.1%) patients in the experimental arm and 13 (22.0%) patients in the control arm were censored at the time of data cutoff and not included in the analysis.

No difference was observed between arms for OR rate, and median DOR was not met on either arm. Clinical benefit rates were not calculated.

Safety

The observed safety profile was consistent with the expected toxicities for seribantumab, which were well manageable.

Biomarkers

HRG mRNA was identified as a biomarker for potential seribantumab efficacy when given in combination with exemestane. For patients with high HRG mRNA, median PFS was 3.82 months, as compared to 1.85 months on placebo plus exemestane. This difference exhibited a strong trend in favor of seribantumab with a HR of 0.26 (95% CI [0.11-0.63]) and p = 0.003.

Immunogenicity

No significant findings were observed.

Pharmacokinetics

Seribantumab PK analysis showed accumulation and achievement of steady state between Cycles 4 and 5. The PK data were consistent with established PK findings.

Overall Summary

The addition of seribantumab to exemestane did not lead to a statistically significant improvement in PFS in the Safety population. Of note, positive trends were observed in patients receiving the combination therapy who were naïve and, as such, sensitive to aromatase inhibitor therapy, as well as in those patients whose tumors tested positive for HRG. This is consistent with the development hypothesis for seribantumab where baseline sensitivity to the combination drug, in this case exemestane, is proposed to be important for achieving an efficacious response in patients with HRG+ tumors.

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