2 SYNOPSIS

NAME OF COMPANY Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** Modrenal® **NAME OF ACTIVE INGREDIENT** Trilostane [(4α,5α,17β)-4,5-epoxy-3,17-dihydroxyandrost-2-ene-2-carbonitrile]	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**
TITLE OF STUDY: A Phase II, Non-Randomised, Study of Modrenal® (Trilostane) in Pre-menopausal Women with Oestrogen Receptor Positive Breast Cancer who have Relapsed or Progressed during or following Prior Hormonal Therapy		
PUBLICATION (REFERENCE): Not applicable		
STUDIED PERIOD: The first patient to enrol in the study was on 08 September 2005 and the last patient to exit from the study was on 21 February 2007.		
PHASE OF DEVELOPMENT: This was a Phase 2 study.		
OBJECTIVES: The primary objective of the study was to determine the clinical benefit rate (CBR) defined as the proportion of patients with a disease response or stabilisation [Response Evaluation Criteria in Solid Tumors (RECIST) criteria] of up to 6 months treatment with Trilostane 720 mg and concomitant hydrocortisone 20 mg in pre-menopausal women with oestrogen receptor (ER) positive breast cancer who have relapsed or progressed during or following prior hormonal therapy. The secondary objectives of the study were to determine objective tumour response, toxicity, time to progressive disease (PD), duration of response, and performance status.		
METHODOLOGY: This was a non-randomised, open-label, Phase 2 study of Trilostane in pre-menopausal women with ER positive breast cancer who relapsed or progressed during or following prior hormone therapy. After screening, eligible patients received daily oral Trilostane, initially following a dose escalation schedule (3 days Trilostane 120 mg, 3 days Trilostane 240 mg and 3 days Trilostane 480 mg) followed by a stable dose of Trilostane 720 mg. Patients also received daily oral hydrocortisone 20 mg throughout the treatment period. Patients received study treatment until PD, unacceptable toxicity, or until the patient was prescribed alternative anti cancer treatment but were observed within the study for 1 year after the study start. Patients were to be evaluated according to the schedule of events at 3 and 6 months, with a confirmatory visit 4 weeks after these visits to confirm response, if needed. Patients were allowed to receive study medication after the end of the treatment period at the investigator's discretion. Patients who continued treatment were followed on a regular basis and all SAEs were to be reported to Bioenvision and/or their representative within 24 hours of initial notification. A two-stage design was used which allowed the study to be stopped after the first stage, if it was considered unlikely that the hypothesised clinical benefit were to be observed after further recruitment.		
NUMBER OF PATIENTS (PLANNED AND ANALYSED): A total of 44 patients were planned to be enrolled with 21 evaluable patients for stage 1 and 20 evaluable patients for stage 2. A total of 5 patients were screened and 4 patients were enrolled and considered evaluable in terms of efficacy and safety.		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

1. Patients must have provided written informed consent prior to any study procedures being performed and according to local ethics committee guidelines.
2. Female patients aged over 18 years.
3. Patients who were assessed by their treating physician as being pre-menopausal. Patients must have been on effective non-hormonal contraception.
4. Patients must have had a histological diagnosis of ER positive breast cancer and have relapsed or progressed during or following prior hormone therapy.
5. Patients must have had performance status ≤2 Eastern Cooperative Oncology Group (ECOG) scale.
6. Patients must have been suitable for hormone therapy in the investigator's opinion. Patients whose disease never responded to any prior hormone therapy (rapid progression on all prior hormone therapies) should not have been entered.
7. Patients must have had a life expectancy of >3 months.
8. Patients may have had measurable (according to RECIST criteria) or without measurable disease at baseline. Patients with bone metastases were only eligible provided that they had evaluable sites of metastases that could be followed by bone scan, X-ray, or magnetic resonance imaging (MRI)/ computerised tomography (CT) scan. Patients without measurable disease at baseline were evaluable for the primary endpoint, CBR, but not for response or duration of response. In these patients, CBR was defined as no progression at the 3 and 6 month assessments
9. Patients must have received at least one prior hormonal therapy in the adjuvant or advanced disease setting.
10. Patients must have had haemoglobin ≥9.0 g/dL (after transfusion if needed) at Screening.
11. Patients must have had a white blood cell (WBC) count ≥3500/mm^3 at Screening.
12. Patients must have had neutrophils ≥1500/mm^3 at Screening.
13. Patients must have had platelets ≥100,000/mm^3 at Screening.
14. Patients must have had a creatinine ≤1.5 x upper limit of normal (ULN) for the testing laboratory, or a creatinine clearance ≥60 mL/minute at Screening.
15. Patients must have had serum bilirubin ≤1.5 mg/dL at Screening.
16. Patients must have had aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) ≤2 x ULN, or if liver metastases was diagnosed by ultrasound or MRI scan ≤5 x ULN at Screening

Exclusion Criteria:

1. Patients who had inflammatory breast cancer.
2. Patients who had concurrent medical or psychiatric problems, unrelated to breast cancer, which would have significantly limited full compliance with the study or exposed the patient to extreme risk or decreased life expectancy.
3. Patients who had hypocortisolaemia.
4. Patients who had received treatment with another investigational therapy within 30 days prior to entry into the study.
5. Patients who were presently receiving or expecting to require concurrent chemotherapy, immunotherapy, radiotherapy or chronic systemic corticosteroid therapy. Patients who had received prior chemotherapy were eligible, provided they had recovered from the acute reversible effects of chemotherapy (generally at least 3 to 4 weeks is required).
6. Any condition which, in the opinion of the investigator, made the patient unsuitable for entry into the study.

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7. Patients who had brain metastases.
8. Patients who had severe concurrent illness.
9. Patients who had previously participated in the study.
10. Patients with known adrenal insufficiency.
11. Patients who were pregnant or nursing.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER: Trilostane 120 mg capsules taken orally; Batch No. [redacted]

DURATION OF TREATMENT: Patients received study medication until PD, unacceptable toxicity, or until the patient was prescribed alternative treatment, if these occurred early); 6-month follow-up if PD was not noted. Patients who continued treatment were followed on a regular basis and all SAEs were to be reported to Bioenvision and/or their representative within 24 hours of initial notification.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Not applicable

CRITERIA FOR EVALUATION: The sponsor (Bioenvision,) decided not to pursue the studied indication because of failure to reach the target enrollment number of patients due to unsatisfactory recruitment, and therefore the data collected will be presented as an abbreviated clinical study report in which the safety and safety-related secondary efficacy results are discussed. Efficacy results will only briefly be summarized but all efficacy data are provided in listings.

Safety Variables: Serious and non-serious adverse events, vital signs including body weight and body mass index; physical examination, clinical laboratory test (haematology, biochemistry, urinalysis; and endocrinology), incidence and severity of toxicity [using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0], and chest X-rays and other imaging procedures.

STATISTICAL METHODS: The statistical methods are described in the final Statistical Analysis Plan.

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SUMMARY – CONCLUSIONS

Safety Results: There were no deaths or no serious adverse events (SAEs) reported in the study. No patients withdrew from the study because of an AE. One patient, Patient [redacted] who had a history of diabetes mellitus, had a clinically significant elevation in urine glucose levels and an AE of CTCAE Grade 1 blood glucose fluctuation that was considered by the investigator to be unrelated to study medication. This AE started on Day 8 and continued throughout the study and was ongoing at Study Exit. This patient did not discontinue the study because of this AE and received therapy for 442 days.

The four evaluable patients in this study experienced 45 AEs and 24 drug-related (possible, probable, and definitely) AEs. The three most common AEs experienced by patients were diarrhoea (2 patients, 4 incidences, 3 incidences considered by the investigator to be drug-related); dyspnoea (3 patients, 3 incidences, 1 incidence considered drug-related); and abdominal pain (2 patients, 3 incidences, 1 incidence considered drug-related). There was one AE of CTCAE Grade 3 toxicity, dyspnoea, which was considered by the investigator to be unlikely related to study medication and was ongoing at the Study Exit visit. There were five AEs of CTCAE Grade 2 toxicity: diarrhoea, gastro-oesophageal reflux disease (GERD), pharyngolaryngeal pain, dyspnoea, and chest wall necrosis. Pharyngolaryngeal pain and chest wall necrosis were considered by the investigator to be unrelated to study medication; the remaining CTCAE Grade 2 AEs were considered possibly or probably related to study medication. All CTCAE Grade 2 AEs were resolved except for dyspnoea and chest wall necrosis, which were ongoing at Study Exit visit. The remaining AEs were CTCAE Grade 1 toxicities. Interestingly, Patients [redacted], [redacted], and [redacted] experienced either nasal or oral burning sensation or paraesthesia that were all considered by the investigator to be related (possibly, probably, or definitely) to study medication and all incidences were resolved while the patients were receiving study medication.

Efficacy: The efficacy results were not analysed because of the early termination of the study and because only four evaluable patients enrolled in the study. All efficacy results were assessments by the investigators.

Clinical benefit and objective tumour response were both considered missing for all patients, except for Patient [redacted] at Week 13 where the objective tumour response was "no". Patients [redacted] and [redacted] had a best overall tumour response of SD at Weeks 13, 26, and 39. Patient [redacted] had a best overall tumour response of SD at Week 13. All but Patient [redacted] had an overall tumour response of PD at Study Exit; Patient [redacted] had an overall tumour response of SD at Study Exit. Two patients had similar time to progressive disease: 63 weeks (censored) for Patient [redacted] and 56 weeks for Patient [redacted]. Patients [redacted] and 12-002, who withdrew from the study due to disease progression, had time to progressive disease of 18 and 11 weeks, respectively.

Conclusion: [redacted]