2. SYNOPSIS

NAME OF COMPANY Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 **NAME OF FINISHED PRODUCT** Modrenal® **NAME OF ACTIVE INGREDIENT** Trilostane	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE OF STUDY:

A Phase IV Non-randomised Study of Modrenal® (Trilostane) in Post-menopausal Women with Advanced, Oestrogen Receptor (ER) Positive Breast Cancer for whom Prior Endocrine Therapies have Failed, One of which was an Aromatase Inhibitor (AI).

INVESTIGATORS/STUDY CENTRES:

Patients were enrolled at 7 centres in the United Kingdom (UK).

PUBLICATION (REFERENCE):

Not applicable

STUDIED PERIOD:

First Patient Enrolled: 29 June 2005

Last Patient Completed: 12 February 2008

PHASE OF DEVELOPMENT:

Phase IV

BACKGROUND

This BIOV-221 study was originally sponsored and initiated by Bioenvision Ltd who contracted Covance CAPS Ltd to conduct and manage all aspects of the clinical study. Genzyme Corporation acquired Bioenvision Ltd on 23 October 2007 and thereby assumed responsibility for Modrenal®. Genzyme has continued to contract all data management aspects of the BIOV-221 study to Covance, except pharmacovigilance which involved Quintiles.
Though this study completed with full patient enrolment, the data are presented as an abbreviated clinical study report as insufficient patients (only 1 patient was eligible) were evaluable for the primary endpoint. This was primarily due to patients not completing the 3 and 6 months assessments and subsequent confirmation assessments to be evaluated for clinical benefit rate to be assessed according to Response Evaluation Criteria in Solid Tumours (RECIST). This abbreviated report focuses on discussing the primary endpoint result and safety of Modrenal (trilostane) in post-menopausal women with advanced, ER positive breast cancer for whom prior endocrine therapies have failed, one of which was an AI.

OBJECTIVES:

Primary Objective:
The primary objective was to determine with a specified level of precision the clinical benefit rate (CBR) of up to 6 months treatment with trilostane 720 mg and concomitant hydrocortisone 20 mg in post-menopausal women with advanced, ER positive breast cancer for whom prior endocrine therapies have failed, one of which was an AI.

Secondary Objectives:

1. To determine objective tumour response
2. To determine toxicity
3. To determine time to progressive disease (PD)

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4. To determine duration of response
5. To determine performance status

METHODOLOGY:

This was a Phase IV, non-randomised, open-label, study of trilostane in post-menopausal women with advanced, ER positive breast cancer for whom prior endocrine therapies have failed, one of which was an AI.

After screening, eligible patients received daily oral trilostane. Patients initially followed a 9-day 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 for the remainder of the study. Patients also received daily oral hydrocortisone 20 mg throughout the treatment period.

Patients received study medication until PD, unacceptable toxicity or the patient was prescribed alternative anti-cancer treatment. Patients were evaluated according to the schedule of events at 3 and 6 months with a confirmatory visit 4 weeks after the 3 and 6-month visit if necessary to confirm response. Patients who did not have PD after 6 months' treatment and who wished to continue study treatment were allowed to do so and observed within the study until a maximum of 1 year after study entry.

This abbreviated study report presents patient information for the one year period after study entry as specified in the protocol.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

A total of 61 evaluable patients were estimated to be required for this study. This was based on a target CBR of 35% based on previous study results ([redacted]). The CBR was be estimated to within 12% of either side (i.e., 95% CI between 23% and 47%). A previous trilostane study had an objective response rate of 38% with 95% CI between 21% and 56% ([redacted]). Therefore, the level of precision required for this study was within these limits.

An additional 5% allowance was made for non-evaluable patients; hence, 63 patients were planned to be assigned to study treatment.

A total of 64 patients were treated and 1 patient completed the study through Week 52.

The full analysis set (FAS) which consisted of all patients who received at least one dose of study treatment (trilostane), was considered the primary analysis population.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Subjects who met all of the following inclusion criteria were eligible to participate in this study:

1. Patients must provide 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 must be assessed as being post-menopausal by the investigator.
4. Patients must have histological diagnosis of ER positive breast cancer and have relapsed or progressed during or following prior hormone therapies, one of which must have been a new generation AI (letrozole, exemestane or anastrozole), prior to Screening

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5. Patients must have performance status ≤2 ECOG scale
6. Patients must be 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 be entered
7. Patients with a life expectancy of >3 months
8. Patients may have measurable (according to RECIST criteria) or without measurable disease at baseline. Patients with bone metastases only are eligible provided that they have evaluable sites of metastases that can be followed by bone scan, x-ray, or MRI/CT scan. Patients without measurable disease at baseline are evaluable for the primary endpoint, CBR, but not for response or duration of response. In these patients CBR is defined as no progression at the 3 month and 6 month assessment.
9. Must have received at least two prior hormonal therapies in the adjuvant or advanced disease setting and not be considered suitable for further treatment with these agents (e.g. due to disease progression during therapy)
10. Patients must have haemoglobin ≥9.0 g/dL (after transfusion if needed) at Screening
11. Patients must have a white blood cell (WBC) count ≥3,500/mm3 at Screening
12. Patients must have neutrophils ≥1,500/mm3 at Screening
13. Patients must have platelets ≥100,000/mm3 at Screening
14. Patients must have 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 serum bilirubin ≤1.5 mg/dL at Screening
16. Patients must have aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) ≤2 x ULN, or if liver metastases by ultrasound or magnetic resonance imaging (MRI) scan ≤5 x ULN at Screening

EXCLUSION:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. Patients with inflammatory breast cancer
2. Patients with concurrent medical or psychiatric problems, unrelated to breast cancer, which would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy
3. Patients who are hypocortisolaemic
4. Patients who have received treatment with another investigational therapy within 30 days prior to entry into the study
5. Patients who are presently receiving or expect to require concurrent chemotherapy, immunotherapy, radiotherapy or chronic systemic corticosteroid therapy. Patients who have received any prior chemotherapy are eligible, provided they have recovered form 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, makes the patient unsuitable for entry into the study
7. Patients with brain metastases

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8. Patients with severe concurrent illness
9. Patients who previously participated in the study
10. Patients with known adrenal insufficiency

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Trilostane was supplied as capsules containing 120 mg active drug. Hydrocortisone was supplied as tablets containing 10 mg active drug. The batch number of trilostane 120 mg capsules used in this study were 014 and 018.

Patients initially followed a 9-day dose escalation schedule of trilostane before receiving 720mg trilostane throughout the remainder of the study as described in the table below.

Number of Capsules Taken Each Time	Number of Times per Day (od=once daily, bd=twice daily)	Time Taken (with meal)	Total Daily Dose (mg)	Duration (days)	Study Days
1	od	breakfast	120	3	1-3
1	bd	breakfast + evening meal	240	3	4-6
2	bd	breakfast + evening meal	480	3	7-9
5	bd	breakfast + evening meal	720	as required	10 onwards

Patients were instructed to take trilostane orally with food to reduce adverse events, using the above dose escalation schedule.

DURATION OF TREATMENT:

Patients received study medication until PD, unacceptable toxicity or until the patient was prescribed alternative anti cancer treatment. All patients were followed for the maximum duration of 1 year after study entry except those who had PD. Patients could continue on study treatment indefinitely if indicated.

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

Not applicable for this study.

CRITERIA FOR EVALUATION:

EFFICACY:

Primary: CBR defined as the proportion of patients with any of the following assessments using the Response Evaluation Criteria in Solid Tumours (RECIST criteria) system at both the 3-month and 6-month visits.

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
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Response (CR or PR) was confirmed 4 weeks after both the 3 and 6 month assessment if needed according to the RECIST criteria (e.g. PR at 3 month assessment and CR at 6 month assessment). For patients without measurable disease at baseline, CBR was defined as no progression at the 3-month and 6-month assessment.

Secondary: Objective tumour response defined as the proportion of patients (with measurable disease) with an overall CR or PR at 3 or 6 months using the RECIST system; incidence and severity of toxicity as assessed by the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0); time to PD; duration of response from date of first response to date of PD (in patients with measurable disease); performance status, using Eastern Cooperative Oncology Group (ECOG) scale.

SAFETY:

Safety was evaluated on the basis of serious and non-serious adverse events (AEs); changes in vital signs; body weight; physical examination; clinical laboratory tests including haematology, biochemistry and urinalysis; Clinically significant changes in laboratory parameters, physical examination findings and vital signs were recorded and evaluated as AEs using CTCAE, Version 3.0.

STATISTICAL METHODS:

Due to the abbreviated nature of this report, CRF data is predominantly presented as listings with limited statistical analyses performed. All data derivations for the listings were carried out using the PC SAS system Version 8.2 software package.

EFFICACY:

The effect of trilostane on ER positive breast cancer in postmenopausal women was determined by the proportion of subjects with CBR relative to the number in the FAS. This was summarised for all patients and the data derivations necessary to compute the primary endpoint were presented in individual data listings.

SAFETY:

Adverse events were coded using the standardised Medical Dictionary for Regulatory Activities (MedDRA) version 7.1. All treatment emergent AEs (TEAEs), serious AEs (SAEs), AE leading to withdrawal or death and treatment-related events were summarised. Adverse events were also summarised by severity using the NCI CTC grade.

The incidence and frequency of all TEAEs and all related TEAEs and SAEs were tabulated by System Organ Class (SOC) and preferred term (PT). The incidence and frequency of all TE and treatment-related TE AE by worse NCI CTC grade were also tabulated by SOC and PT in which a patient's most severe event within a category (e.g., treatment regimen, SOC, PT) was counted.

Due to the limitations in haematology and clinical chemistry data, these were produced as listings only

Changes in vital sign parameters (height, weight, temperature, systolic blood pressure, diastolic blood pressure, pulse rate and respiration) were summarised. Changes in vital sign parameters from baseline (most recent value to baseline or screening visits) to the end of the treatment period or last recorded visit were also summarised.

Changes in physical exam from screening visit to final treatment phase visit were summarised.

Chest X-ray and other study imaging procedures were produced as listings only.

Safety data was summarised for subjects in the FAS only.

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SUMMARY – CONCLUSIONS

EFFICACY:

In this study 64 patients were treated with trilostane. Only one patient completed the study assessments through week 52 to be evaluated for CBR. This patient demonstrated clinical benefit (CR or PR) after 6 months of trilostane treatment. Missing information at necessary 3 or 6 months assessments (or confirmatory response assessments 4 weeks) in patients resulted in these patients being recorded as deriving no CBR. Additionally over half of patients (36/64, 57.1%) withdrew from the study prior to 6 months due to disease progression.

SAFETY:

The majority of patients (63/64, 98.4%) experienced a treatment-emergent adverse event (TEAE), the majority of which (315/415 events) were NCI CTC Grade 1 or Grade 2 events in severity. The majority of patients (55/64 patients, 85.9%) experienced TEAEs in the Gastrointestinal Disorders SOC with nausea (35/64 patients), vomiting (30/64) and diarrhoea (25/64) experienced by approximately 40% of patients or more. Other commonly (≥10%) experienced AEs included constipation, abdominal pain, fatigue and rhinitis.
Fifty-four patients (84.4%) experienced related TEAE, the majority of which were NCI CTC Grade 1 (125/195 events) in severity. The majority of patients (47/64, 73.4%) experienced related TEAEs in the Gastrointestinal Disorders SOC with the most frequently reported (>10% patients) preferred terms being: nausea (32/64 patients; 50.0%), diarrhoea (27/64 patients; 42.2%) and vomiting (18/64 patients; 28.1%).
Twenty-two patients (22/64, 34.4%) experienced 39 TE SAE. Overall, there were eight patients who died (NCI CTC Grade 5) during the study.
The safety profile of Modrenal in this study was consistent with that previously reported with trilostane.

CONCLUSION:

[redacted]