SYNOPSIS

Sponsor: **Cougar Biotechnology, Inc**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: **TBD**	**Volume:**	
Name of Active Ingredient: **Abiraterone Acetate**	**Page:**	

Study Title:

COU-AA-001

An open label Phase I/II study to evaluate the safety and efficacy of an oral 17 α - hydroxylase and $C_{17,20}$-lyase inhibitor, abiraterone acetate, administered daily to castrate males with chemotherapy-naïve castration refractory prostate cancer (HRPC) with a rising PSA (prostate specific antigen) despite hormonal therapy

COU-AA-001 EXT

An expanded access open-label study of CB7630 (abiraterone acetate) in patients with advanced prostate cancer who have completed CB7630 clinical study COU-AA-001

Investigator(s) and Study Center(s):

Investigator: Johann De Bono, PhD

Co-Investigators: Dr. Gerhardt Attard
Professor Ian Judson
Professor David Dearnaley
Dr. Chris Parker

Study Center: Institute of Cancer Research, Royal Marsden Hospital, Sutton, UK

Publication (reference): see Appendix 12.1.11

Studied Period:

COU-AA-001

23 November, 2005 (first subject enrolled) to
20 November, 2008 (last subject completed)

COU-AA-001 EXT

20 July, 2007 (first subject enrolled) to
Ongoing

Study Phase: Phase 1/2

Objectives for COU-AA-001:

Primary Objective:

- To evaluate the safety, tolerability, and recommended dose of abiraterone acetate administered orally by continuous once-daily administration in patients with HRPC.
- To evaluate the activity of abiraterone acetate in HRPC at recommended dose. (PSA working group (PSAWG) criteria and, in patients with measurable disease, RECIST criteria was utilized.

Secondary Objectives:

- To evaluate the pharmacokinetic profile of abiraterone acetate
- To determine the effect of abiraterone acetate on the pituitary-adrenal-gonad endocrine axis and on adrenal hormones by evaluating serum levels of testosterone and its precursors
- To estimate duration of PSA and objective tumor response

Objectives for COU-AA-001 EXT:

Primary Objective:

- To provide access to abiraterone acetate for patients who have completed 12 cycles of abiraterone acetate treatment and continue to receive clinical benefit from such a treatment.

Secondary Objectives:

- To evaluate the safety of abiraterone acetate.
- To evaluate the efficacy of abiraterone acetate.

Methodology:

Both protocols, COU-AA-001 and COU-AA-001 EXT, were open-label, one-arm, single-center studies.

COU-AA-001 consisted of the Dose Escalation Stage (Phase 1) and the Activity Evaluation Stage (Phase 2).

Dose escalation Stage (Phase 1): Based on the conventional three to six evaluable patients per dose cohort used for dose escalation and PK studies, 18 patients participated in this study. The starting dose for the dose escalation phase was 250 mg. If no Common Criteria Terminology for Adverse events (CTCAE) grade 3 toxicity was documented in the first 28 days of continuous daily dosing in a dose escalation cohort, the dose was then escalated to 500, 750, 1000 and finally 2000 mg/day.

Phase 1 also included exploratory Food Effect assessments.

Efficacy (Activity) Evaluation Stage (Phase 2): A two-stage Attained design study was performed. A total of 36 patients with HRPC were recruited to assess the activity of daily continuous abiraterone acetate dosing. The PSA response rate following three cycles, 12 weeks, of abiraterone acetate was determined.

In addition, this study was designed prospectively to allow the addition of dexamethasone (0.5 mg daily) to abiraterone acetate in all patients at disease progression to test the hypothesis that drug resistance could be reversed by suppressing ACTH and the 21 carbon

steroids upstream of the CYP17 drug target in the steroid biosynthesis pathway.

All patients without disease progression after completion of 12 months of therapy (the maximum treatment period in COU-AA-001), were offered the choice to participate in a protocol extension (COU-AA-001 EXT), which permitted continuation of the study medications abiraterone acetate with dexamethasone or prednisolone until disease progression

COU-AA-001 EXT

Patient continued with the same dose/regimen administered at the end of study COU-AA-001 until disease progression or the time when abiraterone acetate (CB7630) became available through local healthcare provider(s) or development programs cease to exist.

Number of Subjects (Planned and Analyzed):

COU-AA 001

Forty-seven patients were planned in the protocol. A total of 54 patients were enrolled.

COU-AA-001 EXT

Thirty patients that completed COU-AA-001 continued on to COU-AA-001 EXT.

From both studies combined, data from 54 patients were analyzed.

Diagnosis and Main Criteria for Inclusion:

For COU-AA-001 the main criterion was patients with chemotherapy-naïve hormone refractory prostate cancer (HRPC) who have failed LHRH analogue and/or antiandrogen therapy.

For COU-AA-001 EXT the main criterion was the patients should have participated in the COU-AA-001 study.

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

Abiraterone acetate administered orally as 250 mg capsules. The lot numbers of abiraterone acetate used for Study COU-AA-001 were 0244A, 0356A, 0063B, 0272B, 0244B, 0357B, 9407001, 0043C, 0079C, 0118C, 0133C, 0180C, 0299C, 0224C, 0113C, and 0252C.

The lot numbers of abiraterone acetate used for Study COU-AA-001EXT were 0133C, 0166C, 0252C, 0299C, 0224C, 0329C, and 0355C.

Duration of Treatment:

Patients in COU-AA-001 were treated for 12 cycles and each cycle was 28 days.
Patients in COU-AA-001 EXT will be treated until CB7630 (abiraterone acetate) becomes available through local healthcare provider(s) or development programs cease to exist.

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

Not applicable

Criteria for Evaluation (COU-AA-001 and COU-AA-001EXT):

Primary for COU-AA-001:

Confirmed, objective PSA (according to PSAWG criteria) response rate resulting from abiraterone acetate therapy. All patients achieving a fall in PSA of >50% from baseline, confirmed by a second measurement at least 4 weeks after, fulfilled the criteria for PSA response

Primary for COU-AA-001EXT

Serum PSA decline evaluation according to PSAWG criteria

Secondary for COU-AA-001:

- Objective response by RECIST criteria (CR/PR) in patients with measurable disease
- Duration of response, by PSA and RECIST criteria
- Time to disease progression, as assessed by time from start of therapy to the onset of the earliest PSA progression and evidence of disease progression according to RECIST criteria
  1. PSA progression as defined by PSAWG
  2. Evidence of disease progression according to RECIST criteria
  3. One bone scan at least 6 months subsequent to baseline demonstrating 2 or more new skeletal lesions
  4. An event due to metastatic prostate cancer requiring intervention (evidence of disease at the site is required
  5. Survival

Safety:

Safety was assessed for adverse events and laboratory data. Safety analyses included all patients enrolled into the study who received at least one dose of abiraterone acetate. Adverse events were summarized by System Organ Class and Preferred Term using MedDRA version 11.0. In addition, adverse events leading to the discontinuation from study were summarized. The severity of AEs was graded on a scale of 1 to 5 according to the NCI Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Shift table analyses for select hematology variables (hemoglobin, hematocrit, platelets, white blood cells, and neutrophils, PT, and PTT) were performed summarizing the number of patients with shifts outside the normal ranges.

Statistical Methods:

All statistical analyses were performed using SAS® version 9 or higher. All confidence interval for the estimation will be reported using 2-sided 95% confidence intervals.

Descriptive statistics were reported for all safety data. Unless otherwise specified, all continuous endpoints were summarized using descriptive statistics, which included the number of patients with a valid measurement (n), mean, standard deviation (SD), median, minimum, and maximum.

All categorical endpoints were summarized using frequencies and percentages. Percentages (e.g. PSA response rate) were calculated by dividing the number of subjects with the characteristic of interest by the number of subjects in the analysis population. The 95% confidence interval was also calculated using the exact (Clopper-Pearson) confidence limits.

Time-to-event endpoints were analyzed using Kaplan-Meier estimates of survival distributions and the median time-to-event. Kaplan-Meier estimates of the median time taken to reach the event was estimated with confidence intervals being calculated using the Brookmeyer-Crowley method.

Pharmacokinetic Variables:

A total of evaluable 12 patients were studied. Patients enrolled in cohorts 1-3 were

administered a single dose of abiraterone acetate on Day -7, with PK blood samples being taken 1, 2, 4, 6, 8, 24, 48 and 72 hours post-dose for analysis and pre-dose on Day 1, Day 8 and Day 15 Cycle 1, Day 1 Cycle 2 and Day 1 Cycle 3.

Patients enrolled in cohorts 4 to 5 were administered two single doses of abiraterone acetate separated by 6 days to evaluate the effects of food on bioavailability.

Summary of Results

Pharmacokinetic:

Following an oral dose of abiraterone acetate at 250 mg (N=3), 500 mg (N=4), 750 mg (N=3), 1000 mg (N=9) or 2000 mg (N=3), no abiraterone acetate was detected *in vivo*.

Abiraterone pharmacokinetic parameters showed variability between patients. Maximum drug concentration (C_{max}) was reached between 1.03 – 6.00 hr post doses across all cohorts. The mean terminal half-life was relatively consistent between cohorts (9.5 – 12.0 hr). Mean clearance values ranged from 494.3 – 1347.2 L/hr. Mean drug exposure (AUC) and C_{max}did not increase linearly with dose.

A significant difference was observed between the administration of drug with or without food (p = 0.004, 1000 mg cohort; p = 0.049, 2000 mg cohort). In the 1000 mg cohort (food effect study) a 2.8 fold difference in mean Cmax drug levels was observed between the dosing regimes, while in the 2000 mg cohort a 3.4 fold difference was observed.

Efficacy:

The primary activity end-point of confirmed PSA response (decline of ≥ 50% from baseline) following three cycles of treatment showed that 60% of the patients had confirmed response. Total (confirmed and unconfirmed) PSA decline of ≥50% was observed in 69.0%.

With regard to the secondary endpoint of maximal PSA response rates approximately 64% of the patients showed ≥ 50% decline in PSA levels.

The median time to PSA Progression was 330 days (95% CI: 197, 530). The median time to PSA response duration was 141 days (95% CI: 85, 235). Post baseline best tumor response for patients with measurable and non-measurable disease was measured. Eight (19.0%) patients showed partial response and 28 (66.7%) patients had stable disease. Two (4.8%) had progressive disease.

Baseline ECOG was 0 in 25 (59.5%) patients. Of the 17 patients with ECOG 1 at baseline, 8/17 (47.1%) improved to ECOG PS 0. All together, 34 patients maintained their ECOG score.

Safety:

In summary, adverse events were reported in 54 (100 %) patients for all the safety population analyzed. The most common (≥ 5%) AEs reported by 53 (98.1%) patients were hypokalaemia experienced by 75.9% (41 patients), fatigue by 46.3 % (25 patients) and hypertension by 33.3% (18 patients). The majority of these adverse events were grade 1 or 2.

In the Dose Escalation Stage, most of the AEs reported by the patients were grade 1 and 2.

Twenty-one patients (38.9%) had grade 3 AEs and three (5.6%) patients had grade 4 AEs. Ten (18.5%) patients had of grade 3 treatment-related AEs and 1 (1.9%) patient had grade 4

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