SYNOPSIS

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Name of Sponsor/Company	Janssen Oncology (formerly Cougar Biotechnology Inc)
Name of Finished Product	ZYTIGA®
Name of Active Ingredient	Abiraterone acetate (CB7630)

Protocol Numbers: COU-AA-001; COU-AA-001EXT

EudraCT Numbers: COU-AA-001: 2005-001166-13; COU-AA-001EXT: 2006-006755-12

MHRA Reference Numbers: COU-AA-001: 25173/0001/001; COU-AA-001EXT: 25173/0001/003

NCT Numbers: COU-AA-001: NCT00473512; COU-AA-001EXT: NCT01664728

Clinical Registry Numbers: COU-AA-001: CR016909; COU-AA-001EXT: CR-016912

Titles of Studies:

COU-AA-001: An open label Phase I/II study to evaluate the safety and efficacy of an oral 17 α -hydroxylase and C17,20-lyase inhibitor, abiraterone acetate, administered daily to castrate males with chemotherapy-naïve castration refractory prostate cancer (CRPC) 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 subjects with advanced prostate cancer who have completed CB7630 clinical study COU-AA-001.

Principal Investigator:

COU-AA-001 and COU-AA-001 EXT: Johann de Bono, M.D., Ph.D. – Institute for Cancer Research, Royal Marsden Hospital, Downs Road, Sutton, U.K.

Publications (Reference):

Attard G, Reid AHM, Yap T, et al. Phase I clinical trial of selective inhibitor CYP17 abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Onc 2008;26:4563-4571.

Attard G, Reid AHM, A'Hern R et al. Selective inhibitor of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Onc 2009;27:3742-3748.

Study Period:

Study COU-AA-001: First subject enrolled 23 November 2005; Last subject completed 20 November 2008.
Study COU-AA-001EXT: First subject enrolled: 20 July 2007; Last subject last visit: 4 September 2012

Phase of Development: 1/2

Objectives for COU-AA-001:

Primary Objectives

- To evaluate the safety, tolerability, and recommended dose of abiraterone acetate administered orally, by continuous once-daily administration in subjects with CRPC.
- To evaluate the activity of abiraterone acetate in subjects with CRPC at recommended dose. Prostate specific antigen working group [PSAWG] criteria and, in subjects with measurable disease, Response Evaluation Criteria in Solid Tumors [RECIST] criteria, were utilized.

Secondary Objectives

- To evaluate the pharmacokinetic (PK) 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 evaluate duration of prostate specific antigen (PSA) and objective tumor response

Objectives for COU-AA-001 EXT:

Primary Objectives

- To provide access to abiraterone acetate for subjects 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 estimate the efficacy of abiraterone acetate

Methods:

The 2 protocols were open-label, single-arm, single-center studies.

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

Dose escalation Stage (Phase 1): Based on the conventional 3 to 6 evaluable subjects per dose cohort used for dose escalation and PK studies, 18 subjects participated in this study. The starting dose for the dose escalation phase was 250 mg. If no NCI (National Cancer Institute) 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, 1,000 and finally 2,000 mg/day.

Phase 1 also included PK assessments and exploratory Food Effect assessments.

Efficacy (Activity) Evaluation Stage (Phase 2): A two-stage attained design study was performed. Twenty subjects with CRPC were recruited to assess the activity of daily continuous abiraterone acetate dosing. The PSA response rate following 3 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 subjects at disease progression to test the hypothesis that drug resistance could be reversed by suppressing adrenocorticotropic hormone (ACTH) and the 21-carbon steroids upstream of the CYP17 drug target in the steroid biosynthesis pathway.

All subjects 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 the protocol extension study (COU-AA-001EXT), which permitted continuation of the study medications abiraterone acetate with dexamethasone or prednisolone until disease progression.

COU-AA-001 EXT

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

Number of Subjects (planned and analyzed):

COU-AA-001

Forty-seven subjects were planned in the protocol. Fifty-four subjects were enrolled.

COU-AA-001EXT

Thirty subjects that completed COU-AA-001 continued onto COU-AA-001EXT. At the time of the data cutoff, for the primary CSR, 13 subjects were ongoing in Study COU-AA-001EXT. At the time of the data cutoff for a previous safety update (22 September 2011), 3 subjects were ongoing.

Diagnosis and Main Criteria for Inclusion:

For COU-AA-001 the main criterion was subjects had CRPC after failure of luteinizing hormone releasing hormone (LHRH) analogue and/or antiandrogen therapy and withdrawal.

For COU-AA-001EXT the main criteria were that subjects had completed 12 cycles of abiraterone acetate treatment in Study COU-AA-001 and were assessed to potentially benefit from continued abiraterone acetate treatment.

Test Product, Dose and Mode of Administration, Batch No.:

Abiraterone acetate administered orally as 250 mg capsules. Following amendment 5 of protocol COU-AA-001EXT, abiraterone acetate could be administered as 250 mg tablets

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, and 0252C.

The lot numbers of abiraterone acetate administered orally as 250 capsules for Study COU-AA-001EXT were 0133C, 0166C, 0252C, 0299C, 0224C, 0329C, and 0355C. The lot numbers of abiraterone acetate administered as tablets were WBB, CFSX, CNTC, and FFHH.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Duration of Treatment:

Subjects in COU-AA-001 were treated for 12 cycles and each cycle was 28 days.

Subjects in COU-AA-001 EXT were to be treated until abiraterone acetate became available through local healthcare provider(s) or development programs cease to exist.

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

<u>Efficacy</u>

Primary: Confirmed, objective response rate (according to PSAWG criteria)ate resulting from abiraterone acetate therapy. All subjects 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

Secondary:

- Objective response by RECIST criteria ([complete response] CR/partial response [PR]) in subjects 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 of the following events:
    1. PSA progression as defined by PSAWG
    2. Evidence of disease progression according to RECIST criteria

Safety

Safety was assessed based on adverse events (AEs) and laboratory data. Safety analyses included all subjects enrolled into the study who received at least 1 dose of abiraterone acetate. Adverse events were summarized by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 11.0. In addition, AEs leading to the discontinuation of treatment were summarized. The severity of AEs was graded on a scale of 1 to 5 according to the adult NCI CTCAE, version 3.0. Shift table analyses for select hematology variables (hemoglobin, hematocrit, platelets, white blood cells, and neutrophils, prothrombin time [PT], and partial thromboplastin time [PTT]) were performed summarizing the number of subjects 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 subjects with a valid measurement (n), mean, standard deviation (SD), median, minimum, and maximum.

All categorical endpoints were summarized using frequencies and percentages. Percentages (eg, 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:

Twelve evaluable subjects were studied. Subjects 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.

Subjects 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.

RESULTS:

Pharmacokinetics:

Following an oral dose of abiraterone acetate at 250 mg, 500 mg, 750 mg, 1,000 mg or 2,000 mg, no abiraterone acetate was detected in vivo. Abiraterone plasma concentrations versus time profiles were indicative of an oral compound for all subjects within and between cohorts. Abiraterone plasma concentrations were detectable up to a minimum of 8 hours postdose and a maximum of 72 hours postdose.

Variation in pharmacokinetic parameters between subjects on the same dose and amongst the dose cohorts may be attributable to metabolic differences between subjects or the rate of drug absorption, particularly as abiraterone acetate is an oral compound.

Abiraterone plasma concentrations were higher when administered concomitantly with food of high fat content, in comparison with fasting. In the 1,000 mg cohort a 2.8 fold difference in mean C_{max} drug levels was observed between the dosing regimens, while in the 2,000 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 3 cycles of treatment showed that 60% of the subjects 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 subjects 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). Postbaseline best tumor response for subjects with measurable and non-measurable disease was measured. Eight (19.0%) subjects showed partial response and 28 (66.7%) subjects had stable disease as the best response. Two (4.8%) had progressive disease as the best response.

Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade was 0 in 25 (59.5%) subjects. Of the 17 subjects with an ECOG of grade 1 at baseline, 8/17 (47.1%) improved to ECOG PS grade 0. Thirty-four subjects maintained their ECOG score.

Safety:

The safety data for Studies COU-AA-001 and COU-AA-001EXT were collected in a single database. Therefore this report is a summary of cumulative safety information from both studies. During the dose escalation phase, no dose-limiting toxicities (DLTs) were reported at any dose level. Cumulative reported AEs in at least 20% of subjects were hypokalemia (81%), fatigue (50%), peripheral edema (45%), hypertension (33%), arthralgia (29%), constipation (26%), musculoskeletal pain (21%), and diarrhea (21%). Most of these events were of toxicity Grade 1 or 2. Eight (19%) subjects discontinued study treatment due to AEs and 5 (12%) of the 8 were treatment related. Adverse events of special interest were mainly due to mineralocorticoid excess resulting from abiraterone acetate treatment (peripheral edema: 45%; hypokalemia: 81%; and hypertension: 33%). Protocol amendments (COU-AA-001, Amendment #5; 24 April 2008; COU-AA-001 EXT, Amendment #3, 19 June 2008) mandated that the treatment regimen include low dose glucocorticoid (prednisone or prednisolone 5 mg twice daily or 0.5 mg dexamethasone once daily) to alleviate the mineralocorticoid excess associated with abiraterone acetate treatment. Two subjects discontinued treatment due to AEs of special interest (Grade 3 hypokalemia [1 subject] and Grade 3 gamma glutamyl transferase [1 subject]).

Serious adverse events were reported in 19 (45%) subjects. Four deaths occurred during the study, 3 of the 4 deaths occurred within 30 days of the last dose of study drug. No death was attributed to an AE assessed as treatment related.

CONCLUSIONS:

- Increased abiraterone acetate exposure was observed with increasing doses. Food aids absorption. Increased variability in pharmacokinetic parameters between subjects on the same dose and amongst the dose cohorts was observed.
- Subjects experienced benefits on abiraterone acetate treatment as demonstrated by the PSA response, tumor response, and improvement or maintenance of performance status.
- During the escalation phase, no DLTs were reported. Most reported AEs were Grade 1 or 2 in severity. Secondary mineralocorticoid excesses resulted in hypokalemia, hypertension, and fluid retention related to the pharmacodynamic effects of abiraterone acetate. The incidence of mineralocorticoid-related toxicities was most likely due to most subjects beginning the study with abiraterone acetate as monotherapy. Although corticosteroids were not mandated at the initiation of the study, the incidence of adverse events related to mineralocorticoid excess with abiraterone acetate monotherapy was of sufficient frequency to support the routine use of glucocorticoids. These events were addressed by the addition of low-dose prednisone/prednisolone or dexamethasone via protocol amendment in 2008.
- The cumulative median duration of treatment was 14 months and 8 (19%) remained on treatment for at least 27 months. This extended duration of treatment indicate that abiraterone acetate was well tolerated in subjects who had not received chemotherapy and had a rising PSA on hormonal therapy.