SYNOPSIS

TITLE OF STUDY:

An open-label, multi-centre, extension study investigating the long-term safety of repeated doses of FE200486 given as subcutaneous injections to prostate cancer patients

INVESTIGATOR(S):

Principal Investigators were [redacted].

STUDY CENTRE(S):

The nine participating centres in Japan were [redacted].

PUBLICATION (REFERENCE):

None

STUDIED PERIOD (YEARS):

First subject signed consent: 9 May 2005
Last subject last visit: 23 June 2010

PHASE OF DEVELOPMENT:

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OBJECTIVES:

Primary Objective:

- To investigate the long-term safety after repeated doses of FE200486 when given as subcutaneous injections to prostate cancer subjects.

Secondary Objectives:

- To investigate the long-term response with respect to testosterone, prostate-specific antigen (PSA), 5α-dihydrotestosterone (DHT), luteinising hormone (LH) and follicle-stimulating hormone (FSH) after repeated doses of FE200486.
- To investigate the population pharmacokinetic (PK) and pharmacodynamic (PD) relationship in terms of testosterone suppression after repeated doses of FE200486.

METHODOLOGY:

This was an extension to an initial study, Study FE200486 CS11 (Study CS11; a single dose, dose-escalating study, evaluating safety and the PK/PD profile of subcutaneous FE200486 in subjects with prostate cancer). In this extension study, subjects continued to be administered subcutaneous FE200486 at the same dose (160 mg, 200 mg or 240 mg, all at a concentration of 40 mg/mL) and frequency (every 4 or 12 weeks) as they had received in Study CS11. Every 4 weeks, subjects returned to the study site for safety assessment and the collection of blood samples for measurements of testosterone, PSA, LH, FSH, DHT, sex hormone-binding globulin (SHBG) and PK/PD variables. Subjects remained in the study unless any of the discontinuation criteria or termination criteria for efficacy such as the following were met:

- Serum testosterone concentration > 1.0 ng/mL measured at any visit at least 28 days after administration of FE200486.
- Serum testosterone concentration ≥ 0.5 ng/mL and ≤ 1.0 ng/mL measured at two consecutive visits at least 28 days after administration of FE200486.
- For any reasons of safety, including a worsening of the subject's condition, as judged by the investigator.

This report presents the results of the final analysis now that all subjects have finished the study.

NUMBER OF SUBJECTS:

Planned: 18 subjects. Studied: 6 subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects with prostate cancer who had completed the initial study (Study CS11) and a suppression of testosterone for at least 28 days, and who had completed the End-of-Study Visit for Study CS11.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:

FE200486 was formulated as powder and solvent for solution. Subjects received repeated doses at the same dose as they had received in the initial study (Study CS11). A subcutaneous injection of FE200486 was administered every 4 or 12 weeks based on the subject's response during the initial study. Subjects who had a suppression of testosterone (i.e., < 0.5 ng/mL) for a period of at least 28 days up to 84 days during Study CS11 were administered FE200486 once every 4 weeks and those who had a suppression for more than 84 days were administered FE200486 once every 12 weeks.

Group	Dose	Route	Concentration	Administration
A	160 mg	subcutaneously	40 mg/mL	2 x 2.0 mL
B	200 mg	subcutaneously	40 mg/mL	2 x 2.5 mL
C	240 mg	subcutaneously	40 mg/mL	2 x 3.0 mL

DURATION OF TREATMENT:

Subjects were to participate in the study until they met a pre-defined discontinuation criterion, or until FE200486 was approved in Japan or a decision made to end development of the compound.

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

There was no reference therapy in this study.

CRITERIA FOR EVALUATION:

Primary:

- Frequency and severity of adverse events (AEs);
- Local injection-site reactions;
- Safety laboratory parameters (haematology, biochemistry, urinalysis);
- Vital signs and 12-lead electrocardiogram (ECG).

Secondary:

- Time to testosterone escape;
- Plasma FE200486 concentration at visit before time of testosterone escape;
- Time course of testosterone, PSA, LH, FSH and DHT;
- Population PK/PD parameters;
- Time to disease progression.

STATISTICAL METHODS:

Safety analysis: AEs, safety laboratory values, injection-site reactions, vital signs and 12-lead ECGs were evaluated by descriptive statistics and data listings.
Pharmacodynamic analysis: Descriptive statistics were reported for each treatment group.
Pharmacokinetic analysis: The plasma FE200486 concentration data were listed.

RESULTS:

The results of this extension study were based on the final analysis conducted at the completion of the study, i.e., once all subjects had discontinued the study. As there were only six subjects, no meaningful comparison between FE200486 doses could be made in the analysis of safety and efficacy.

- Of the six subjects enrolled, four subjects withdrew from the study due to rising PSA levels; one subject switched to another treatment; and the final subject withdrew due to a serious adverse event (SAE) of colon cancer.

SAFETY RESULTS:

- Six subjects received between 1 and 18 subcutaneous injections of FE200486 every 12 weeks.
- One SAE (colon cancer; considered by the investigator to be unrelated to study medication) was reported which led to withdrawal from the study.
- Six subjects reported at least one treatment-emergent AE (TEAE) and all subjects also had at least one TEAE that was considered by the investigator to be either possibly or probably related to study medication.
- One TEAE was classified as severe in intensity (SAE of colon cancer); the majority of TEAEs were mild.
- The most commonly reported TEAEs were those related to laboratory abnormalities (low haemoglobin, haematocrit and red blood cell count) and injection-site reactions (erythema, nodule and sclerosis), all of which were mild.
- Four subjects reported at least one mild testosterone suppression symptom (hot flush, hyperhidrosis and/or fatigue).
- No conclusions could be drawn from the safety laboratory data.
- There were no findings of note in vital signs or 12-lead ECG data.

EFFICACY RESULTS:

- No subject reached the testosterone escape level (testosterone of > 0.5 ng/mL at one visit from Day 28 onwards).
- No subject reached the insufficient testosterone response criteria (testosterone > 1.0 ng/mL or two consecutive visits with testosterone > 0.5 ng/mL from Day 28 onwards).
- Three subjects showed disease progression (an increase in serum PSA of more than 50% from nadir in Study CS11A and at least 5 ng/mL, from Visit 2) at 56, 112 and 420 days.
- Six subjects experienced a 50% reduction in PSA values from baseline at 28 or 56 days and two subjects (one in the 200 mg group and one in the 240 mg group) experienced a 90% reduction in PSA values from baseline.
- Four subjects withdrew from the study due to rising PSA levels.

CONCLUSIONS:

FE200486 was administered subcutaneously to six subjects with prostate cancer at doses of 160 mg, 200 mg or 240 mg every 12 weeks for between 0 and 47.6 months. The FE200486 subcutaneous administration was well tolerated.