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SYNOPSIS

Study Title: A Phase 1/2, Open-Label Study in Men With Prostate Cancer to Assess the Safety, Pharmacokinetics, and Testosterone-Lowering Efficacy of TAK-448, Administered as a 1-Month Depot, Including a Randomized Portion With a Group Administered Leuprorelin

Investigator(s): PPD

Study Center(s): There were 5 active centers in France that recruited patients.

Publication (reference): None

Study Period: 15 November 2010 to 09 September 2011 **Phase:** 1/2

Initiation Date (first patient enrolled): 15 November 2010 (date of first dose)

Early Termination Date: 25 August 2011

Completion Date (last patient completed): 09 September 2011

Study Objectives:

Primary Objective: Phase 1, Single-Dose

- To assess the safety and pharmacokinetics (PK) of TAK-448 in patients receiving a single-dose of 1-month depot TAK-448.

Secondary Objective: Phase 1, Single-Dose

- In patients not receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy, to assess the effect of single-dose 1-month depot TAK-448 on serum testosterone, serum luteinizing hormone (LH), and serum prostate-specific antigen (PSA) concentrations.

Exploratory Objective: Phase 1, Single-Dose

- CCI [redacted]

METHODS

Design:

The phase 1, single-dose portion of this study was an open-label, multicenter, dose-escalation study of 1-month depot TAK-448 in adult male patients with prostate cancer who were either on GnRH therapy or eligible for GnRH therapy in the foreseeable future. On 25 August 2011, the study was stopped early due to an unacceptable PK profile of the formulation; therefore, the phase 1, multi-dose and phase 2 portions of the study were not conducted CCI [redacted].

In the phase 1, single-dose portion of this study, enrollment was expected to achieve 3 evaluable patients in each of the 4 planned dose-level cohorts and in each of any potential additional dose-level cohorts. All patients were to receive a dose of TAK-448 and in the first 2 cohorts only placebo at contralateral abdominal sites via subcutaneous injection; study drug was to be administered on the right side for all patients and placebo (if applicable) on the contralateral side (ie, the left side) to facilitate the evaluation of any injection site reactions. Prior to opening a cohort at a higher dose level, available Day 1 PK and 30-day safety data were reviewed. Based on PK and safety findings at these dose levels, additional patients could be enrolled to accommodate additional dose-level cohorts

and expansion of 1 or more cohorts to better characterize PK and safety. Following the depot doses, patients were followed at regular intervals for blood sampling and assessments of safety, tolerability, and other endpoints. Patients attended the End-of-Study visit approximately 3 months (± 5 days) after study drug administration.

Serial blood specimens at prespecified time points were obtained from all patients for determination of the PK plasma concentrations and endocrine pharmacodynamic (PD) effects of TAK-448. Serum PSA concentrations were also determined in phase 1. Cohort 3 (24-mg dose group) criteria were modified so that only hormone therapy-naïve patients were included in the cohort. Adverse events (AEs) were assessed, and laboratory values (chemistry, hematology, and urinalysis), vital signs, physical examinations, and electrocardiograms (ECGs) were obtained to evaluate the safety and tolerability of TAK-448.

Number of Patients (planned and analyzed):

Up to 30 patients were planned to be enrolled in the phase 1, single-dose portion of the study. Actual enrollment achieved 9 evaluable patients, 3 in each of the 6-mg, 12-mg, and 24-mg dose groups.

Diagnosis and Main Criteria for Inclusion:

Male patients with prostate cancer aged 40 to 78 years were enrolled. Patients completed their primary treatment for prostate cancer at least 6 months prior to screening and were either on GnRH therapy or were a potential future candidate for GnRH therapy (ie, in a period of "watchful waiting"). GnRH-naïve patients were required for cohort 3 (24-mg dose group) in order to evaluate testosterone and PSA responses. Patients were to have generally indolent or stable disease with PSA-doubling time > 4 months if on GnRH therapy (including intermittent therapy) or PSA-doubling time > 3 months if not on GnRH therapy, and screening serum PSA concentration > 2 ng/mL (absolute PSA < 200 ng/mL), unless the patient was on concurrent or intermittent GnRH analog therapy, in which case, no lower limit was applicable. Patients with recurrent local disease were to be generally asymptomatic, without bladder, bowel, or obstructive symptoms. Patients with metastatic disease were to be asymptomatic and with only bone scan positive and/or lymph node evidence of metastases. Patients with prior surgical castration were to be excluded.

Test Product, Dose and Mode of Administration:

TAK-448; 6 mg, 12 mg, and 24 mg by subcutaneous injection; batch number: Z369901.

Duration of Treatment:

Patients were to be administered a single dose of a depot formulation of TAK-448 and a single dose of placebo (first 2 cohorts only).

Reference Therapy, Dose and Mode of Administration:

Placebo (which included all of the components of the active formulation except for TAK-448); by subcutaneous injection; batch number: Z369A01.

Pharmacokinetic Assessments:

Primary Endpoints: Phase 1, Single-Dose

Day 1: maximum observed plasma concentration (C_{max}), area under the plasma TAK-448 concentration curve on Day 1 ($AUC_{0\text{-}24hr}$), area under the plasma TAK-448 concentration curve through Day 29 ($AUC_{0\text{-}29d}$), area under the plasma TAK-448 concentration curve to the time of last quantifiable concentration ($AUC_{0\text{-}last}$), first time to maximum observed plasma concentration (T_{max}), and time to last quantifiable concentration (T_{last}).

Pharmacodynamic Assessments:

Secondary Endpoints: Phase 1, Single-Dose

In patients not on concomitant GnRH therapy, serum testosterone and LH concentrations, proportion of patients with serum testosterone concentration below the castrate level (≤ 50 ng/dL, < 1.74 nmol/L) after 29 days, and serum PSA concentrations.

Exploratory Endpoints: Phase 1, Single-Dose

CCI [redacted]

Efficacy Assessments:

The exploratory endpoints above were surrogate efficacy endpoints.

Safety Assessments:

Primary Endpoints: Phase 1, Single-Dose

Vital signs, 12-lead ECGs, injection site-related skin reactions, AEs, and serious adverse events (SAEs).

Statistical Methods:

Statistical analyses for the phase 1 portion of the study are primarily descriptive and graphical in nature.

RESULTS

Demographic Results:

Nine patients were enrolled in the study, 3 in each dose group (6 mg, 12 mg, and 24 mg), and all 9 patients were included in the Safety and PK Populations. Per the protocol, 4 dose levels were planned in an escalating order (planned doses: 6 mg, 15 mg, 30 mg, and 60 mg). Based on review of the relevant PK and safety data, actual doses in the escalation sequence were adjusted to levels that were lower than the proposed levels in the protocol (actual doses: 6 mg, 12 mg, and 24 mg). Overall, 4 patients (44%) received concomitant GnRH therapy, 6 patients (67%) received a contralateral placebo injection, and 9 patients (100%) had a valid serum testosterone value at the Month 1, Day 29 visit.

Demographic and other baseline characteristics were similar across the dose groups.

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetic Results

CCI and CCI show mean plasma concentration-time curves by dose group for the Day 1 (up to 12 hours) and the full profile (up to Month 3). A high-burst release of TAK-448 drug concentrations was observed within hours after administration of depot injection. On the basis of pharmacokinetics observed in a prior study, it was estimated that the absolute quantity of TAK-448 released during the first 24 hours approximated 25% of the total administered dose. The $AUC_{0\text{-}24hr}$ comprised over 60% of the $AUC_{0\text{-}last}$ observed showing a significant release of drug from formulation. Drug concentrations were very low over the next several days followed by a slow rise, suggesting delayed and slow release from the formulation. Washout in all cases occurred by 8 weeks after dosing.

Overall, the low plasma concentrations of TAK-448, the delayed release profile over the 1 month following administration, and the high inter-patient variability of the 1-month depot formulation were considered not acceptable for further clinical development.

Pharmacodynamic Results

Below castration levels of testosterone were achieved in 1 out of 2 GnRH-naïve patients at 12 mg and 3 out of 3 patients at 24 mg. Values were recovering during Month 2.

Biomarker Results

Serum PSA response in patients receiving and not receiving concomitant GnRH analog therapy is listed in CCI Corresponding reductions in PSA were observed as a biomarker of testosterone-lowering efficacy and treatment response. A greater than 50% decrease from baseline in PSA was seen at Month 1, Day 29 in 3 out of 3 patients in the 24-mg dose group.

Safety Results:

All 9 TAK-448 patients (100%), 3 in each dose group, experienced at least 1 AE during the study. Overall, the most common TEAEs for all patients were grade 1 injection site reactions: injection site erythema (6 patients, 67%), injection site induration (5 patients, 56%), injection site haematoma (3 patients, 33%), and injection site pain (3 patients, 33%), as well as hot flush (4 patients, 44%). The TEAEs reported only by patients in the highest dose group were asthenia, constipation, weight decreased, and headache (1 patient each).

Eight TAK-448 patients (89%) had a drug-related TEAE, 2 patients in the 6-mg dose group (67%), 3 patients in the 12-mg dose group (100%), and 3 patients in the 24-mg dose group (100%). Related TEAEs consisted of injection site reactions (8 patients, 89%) and hot flush (4 patients, 44%).

There were no grade 3 or higher AEs, no SAEs, and no deaths during the study.

Eight patients (89%) experienced a total of 22 injection site reactions during the study: 7 of 9 patients experienced a total of 17 injection site reactions at the site of TAK-448 injection; 3 of 6 patients experienced a total of 5 injection site reactions at the site of placebo injection.

The initial 6 patients in the 6-mg and 12-mg dose groups each received 1-month depot of TAK-448 and placebo at contralateral abdominal sites to evaluate skin toleration of formulation components excluding TAK-448. Of these 6 patients, 2 each experienced injection site reactions at both the site of the TAK-448 and the placebo injection. Additionally, 2 patients each experienced an injection site reaction at only the TAK-448 injection site, and 1 patient experienced an injection site reaction at only the placebo injection site.

The 5 injection site reactions at the site of placebo injection may have been related to agglomeration of the placebo formulation, which made it difficult to deliver through the syringe. Two such instances resulted in product complaints, and a decision was made to discontinue the application of the placebo formulation CCI

All injection site reactions were grade 1 in intensity and resolved/recovered (except for 1 report of injection site erythema that resolved/recovered with sequelae [not specified]). Most injection site reactions were considered treatment related except for injection site haematoma, injection site induration, and injection site erythema experienced by 1 patient in the 12-mg dose group at the placebo injection site.

One patient had a TEAE that involved an individual laboratory abnormality during the study. One patient in the 12-mg dose group experienced grade 2 elevated cholesterol (hypercholesterolaemia), which was considered not related to study drug.

There was no apparent dose-related trend for change in on-study maximum observed values for vital signs; however, there was a decrease in absolute values of minimum vital sign values, which included changes from baseline in mean supine and standing systolic and supine diastolic blood pressure and a decrease in temperature. For individual abnormalities in vital signs, 1 patient had hypertension (reported as a TEAE) and 1 patient had hypothermia (ie, a reduction in body temperature below 35°C).

A possible dose-related trend was observed in maximum on-study mean changes in ECG parameters, which showed a decrease in QTcF and PR by ascending dose. For individual abnormalities, 6 patients, 2 in each dose group, had abnormal ECG findings during the study; however, none were considered clinically significant. Two patients had an ECG change of nonclinical significance of atrioventricular block first degree reported as a TEAE during the study; both were assessed as grade 1 and not related to study drug.

CONCLUSIONS:

- TAK-448 was well tolerated up to 24 mg as a single depot injection in this population of patients with prostate cancer during this study.
- TAK-448 plasma concentrations peaked rapidly following depot administration, followed by a rapid decline in concentrations. After the first 48 hours, concentrations increased slowly following a slow release of TAK-448 from the depot formulation.
- The 1-month depot formulation of TAK-448 showed the potential to lower serum testosterone to below the castrate level for patients in the 24-mg dose group.
- The 1-month depot formulation did not meet the PK criteria necessary for further development.

Date of Report: 18 September 2012