Name of Company: Mitsubishi Tanabe Pharma Corporation
Volume: (For national authority use only)
Name of Finished Product: MCI-196
Page:
Name of Active Ingredient(s): MCI-196

Title of Study: A Phase III, Double-blind, Multi-centre, Randomised, Parallel Group Design, Placebo-controlled, Flexible Dose Study of MCI-196 in Combination with a Calcium-based Phosphate Binder in Chronic Kidney Disease Stage V Subjects on Dialysis with Hyperphosphataemia

Protocol Number: MCI-196-E09

Coordinating Investigator:
[redacted]

Study Centres: The study was conducted at 10 sites in the Czech Republic, Italy, Poland and United Kingdom.

Publication(s): None.

Studied Period: **Phase of Development:** III
Date of first subject screened: [redacted]
Date of last subject completed:
Date of early study termination:

Objectives:
The primary objective of this study was to demonstrate the additive effect of MCI-196 in the control of hyperphosphataemia (in chronic kidney disease [CKD] stage V subjects on dialysis) when combined with a low dose of a calcium-based phosphate binder. All subjects were treated with a low dose of a calcium-based phosphate binder and, in addition, were randomised to receive either MCI-196 or placebo.
The secondary objectives of this study were:

- To demonstrate superiority of MCI-196 over placebo in the control of other efficacy parameters (such as serum low density lipoprotein cholesterol [LDL-C], other lipid parameters, serum intact parathyroid hormone [iPTH], serum calcium, and serum calcium x phosphorus ion product [Ca x P]) in subjects with stage V CKD on dialysis.
- To assess the safety and tolerability of flexible dose MCI-196.

Study Design:
This was a phase III, multi-centre, double-blind, placebo-controlled, randomised, parallel group study comparing MCI-196 in combination with a calcium-based phosphate binder versus placebo in combination with a calcium-based phosphate binder.
The study comprised 2 periods: the calcium-based phosphate binder run-in period (of up to 4 weeks) and the double-blind treatment period (of 12 weeks).
During the calcium-based phosphate binder run-in period, the subject's dose of calcium-based phosphate binder was reduced to, or maintained at, a dose between 0.5 and 1.0 grams (g) per day (inclusive) elemental calcium, at the investigator's discretion, and fixed for that subject for the duration of the study. No study medication was administered during the calcium-based phosphate binder run-in period.
Eligible subjects then entered the 12-week double-blind treatment period. Subjects were randomised to receive either MCI-196 or placebo in addition to the reduced dose of calcium-based phosphate binder achieved during the run-in period.
During the treatment period, subjects were seen once weekly for 12 weeks.

Name of Company: Mitsubishi Tanabe Pharma Corporation	**Volume:**	(For national authority use only)
Name of Finished Product: MCI-196	**Page:**	
Name of Active Ingredient(s): MCI-196		

Number of Subjects (planned and analysed):

The target enrolment was 200 subjects (100 subjects per treatment group). The target minimum recruitment for each site was to be 10 subjects.

The study was prematurely terminated by the Sponsor on [redacted] due to difficulties in recruitment. Over a 2-year period, only 41 subjects were screened, of which 35 subjects were screening failures. A total of 6 subjects were randomised, of which 4 completed the study.

Diagnosis and Main Criteria for Inclusion:

Subjects had CKD stage V, as defined by the Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines. Other main inclusion criteria were:

- Informed consent.
- Male or female, 18 to 80 years of age.
- Clinically stable on haemodialysis or peritoneal dialysis for at least 3 months (as judged by the investigator).
- Stable phosphate control (as judged by the investigator) using phosphate binders for at least 3 months. For subjects on calcium-based phosphate-binding medication only, current treatment had to contain a dose of ≥1.0 g per day elemental calcium (i.e., equivalent to ≥2.5 g per day of calcium carbonate or ≥4 g per day of calcium acetate). For subjects on calcium-based phosphate-binding medication in combination with non-calcium-based phosphate-binding medication, current treatment had to contain a dose of ≥0.5 g per day elemental calcium (i.e., equivalent to ≥1.25 g per day of calcium carbonate or ≥2 g per day of calcium acetate).
- Regular dialysis treatment:
  - If the subject was on haemodialysis, this was scheduled to occur 3 times per week in a hospital or centre setting. The duration had to be between 3 to 5 hours, or if high-flux dialysis a minimum of 2.5 hours, depending on the standard of care in each centre.
  - If the subject was on peritoneal dialysis, this was scheduled to be either daily automated peritoneal dialysis or continuous ambulatory peritoneal dialysis, the latter employing at least 3 bag changes per day.
- Serum phosphorus levels <2.26 millimoles (mmol)/litre (L) (7.0 milligrams [mg]/decilitre [dL]) at screening.
- Calcium dialysate content between 1 to 1.75 mmol/L, depending on the standard of care in each centre. Calcium dialysate content was to remain constant for the duration of the study.
- Stabilised phosphorus diet, as considered appropriate by the physician.
- Baseline dialysis adequacy ratio (rate of urea clearance over volume; Kt/V) (single pool) of at least 1.2 for haemodialysis subjects, and a weekly Kt/V value of at least 1.8 for peritoneal dialysis subjects.
- Negative pregnancy test in female subjects of childbearing potential. Appropriate contraception during the course of the clinical study.

Additional criterion for randomisation:

- Serum phosphorus level of ≥1.94 mmol/L (6.0 mg/dL), and at least 15% greater than at screening after completion of the run-in period.
  OR
- Serum phosphorus level ≥2.58 mmol/L (8.0 mg/dL) at any time during the run-in period.

Name of Company: Mitsubishi Tanabe Pharma Corporation	**Volume:**	(For national authority use only)
Name of Finished Product: MCI-196	**Page:**	
Name of Active Ingredient(s): MCI-196		

Test Product, Dose and Mode of Administration, and Batch Number(s):
MCI-196 was provided in 1 g tablets to be taken orally 3 times a day (t.i.d.) with meals.
The starting dose of MCI-196 was 6 g per day. The maximum dose allowed was 15 g per day. No titration was allowed for the first 3 weeks. Titration (up or down) was then allowed every 3 weeks in aliquots of 3 g per day to achieve and maintain serum phosphorus levels <1.78 mmol/L (5.5 mg/dL). Therefore, permissible doses of MCI-196 were 3, 6, 9, 12 or 15 g per day. These doses represent 3, 6, 9, 12 or 15 tablets per day. No intermediate doses were allowed.
MCI-196 blinded batch number assigned by [redacted]

Reference Therapy, Dose and Mode of Administration, and Batch Number(s):
Matching placebo was provided in tablets to be taken orally t.i.d. with meals.
The starting dose and titration rules were as described above for MCI-196. The number of placebo tablets corresponded to the number of MCI-196 tablets (i.e., 3, 6, 9, 12 or 15 tablets per day).
Placebo blinded batch numbers assigned by [redacted]

Duration of Treatment: The duration of treatment was 12 weeks.

Criteria for Evaluation:
Efficacy:
The primary endpoint was the change in serum phosphorus (value from central laboratory) from baseline (Week 0) to Week 12 (or last observation carried forward [LOCF]) for low-dose calcium plus MCI-196 compared to low-dose calcium plus placebo.
Secondary efficacy endpoints included:

- The change from baseline (Week 0) to Week 12 (LOCF) for low-dose calcium plus MCI-196 and low-dose calcium plus placebo in serum calcium, serum Ca x P, serum iPTH and serum uric acid.
- The percentage change from baseline (Week 0) to Week 12 (LOCF) for low-dose calcium plus MCI-196 and low-dose calcium plus placebo in serum LDL-C, serum total cholesterol (TC), serum high density lipoprotein cholesterol (HDL-C) and serum triglycerides (TG).
- The proportion of responders at Week 12 (LOCF) for serum phosphorus, mineral metabolism (serum phosphorus, serum calcium, serum Ca x P and serum iPTH) and serum LDL-C.
- The time to response for reaching serum phosphorus level of ≤1.78 mmol/L (5.5 mg/dL).

Due to the early termination of the study and the small number of subjects evaluable for efficacy, the above criteria were not formally evaluated.

Safety:
Safety endpoints included the incidence of adverse events (AEs) and change from baseline to Week 12/End of study visits in safety parameters (e.g., laboratory values, vital signs, electrocardiogram [ECG] and physical examination).
Due to the early termination of the study, only AE data and concurrent medical history were summarised.

Statistical Methods:
Although a Reporting and Analysis Plan was prepared, only descriptive statistical analyses were performed because the study was prematurely terminated. Data listings and a small number of descriptive statistical tables were prepared for completeness.
The intent-to-treat (ITT) population included all subjects who received a randomisation number, took at least 1 dose of study medication and had at least 1 central serum phosphorus value after the start of study medication. Subjects were included according to the treatment to which they were randomised.
The safety population (SAF population) included all randomised subjects who received at least 1 dose of study medication. Subjects were included according to the treatment they received.

Name of Company: Mitsubishi Tanabe Pharma Corporation	**Volume:**	(For national authority use only)
Name of Finished Product: MCI-196	**Page:**	
Name of Active Ingredient(s): MCI-196		

Efficacy Results:

In this study, only 6 subjects were randomised, thus, mean and median data have limited meaning.
Three subjects received MCI-196 and 3 subjects received placebo. All 3 MCI-196-treated subjects completed the study. In the placebo group, 1 subject completed the 12-week treatment period, 1 subject had serum phosphorus data available at Week 1 and at the end of treatment visit, and 1 subject had serum phosphorus data available up to Week 4 and at the end of treatment visit.
Individual serum phosphorus levels showed a decrease from baseline at the majority of timepoints in MCI-196-treated subjects, but generally increased from baseline in placebo-treated subjects.
No trends could be identified for the secondary efficacy endpoints.

Safety Results:

The majority of subjects in the SAF population reported treatment-emergent AEs (TEAEs) (3 subjects in the MCI-196 group and 2 subjects in the placebo group).
The most common TEAEs overall were gastrointestinal disorders, including nausea (reported by 1 subject in the MCI-196 group and 2 subjects in the placebo group) and vomiting (reported by 1 subject in the placebo group). One subject in the MCI-196 group reported decreased appetite. All of these events were considered to be treatment-related.
No subjects in the MCI-196 group discontinued due to a TEAE. Two subjects in the placebo group had a TEAE leading to discontinuation (nausea and vomiting, respectively).
One subject in the placebo group reported a treatment-emergent serious AE (SAE) of hypertension (verbatim text: worsening of arterial hypertension) which was considered to be treatment-related.
One screening failure subject died due to a fatal SAE of cardiac failure. No randomised subjects died during the study.
No trends or safety concerns could be identified from vital signs, laboratory parameters, physical examination or ECG data.

Conclusions:

The study was prematurely terminated by the Sponsor due to difficulties in recruitment. Only 41 subjects were screened at 10 participating sites, of which 6 subjects were randomised and 4 completed the study.
Due to the limited data available, only descriptive analyses were performed and no conclusions on the efficacy of MCI-196 can be drawn.
Although gastrointestinal disorders are commonly reported with other phosphate binders, in this study gastrointestinal disorders were more common in the placebo group than the MCI-196 group. Nausea was reported by 2 subjects in the placebo group versus 1 subject in the MCI-196 group, and vomiting was reported by 1 subject in the placebo group. No other TEAEs were reported by more than 1 subject.
No safety concerns were identified from the safety data.

Date of Report: [redacted]