2. SYNOPSIS

Name of Sponsor/Company: Reata Pharmaceuticals, Inc., a wholly-owned subsidiary of Biogen	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Bardoxolone methyl		
Name of Active Ingredient: Bardoxolone methyl (RTA 402)		

Title of Study:

A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Investigators: Multicenter, Dr. Pablo Pergola was selected as Principal Investigator for this study. However, due to early study termination and reductions in study site staff, a Principal Investigator's signature is not available for this report.

Study Center(s): Multicenter

Publications (Reference):

None to date.

Studied Period (Years):	**Phase of Development:** 3
First patient consent date: 13 May 2019 Date last patient last visit completed: 08 August 2023 Early termination date: 10 May 2023	

Objectives:

The primary objectives of the study were:

- To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108.
- To assess safety and tolerability.

Methodology:

Study 402-C-1808 (which was also referred to as FALCON) was terminated on 10 May 2023.

This study was an international, multi-center, randomized, double-blind, placebo-controlled Phase 3 trial that assessed the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with autosomal dominant polycystic kidney disease. Approximately 850 patients were planned to be enrolled.

Patients were randomized 1:1 to either bardoxolone methyl or placebo. Randomization was stratified by eligibility eGFR category (30 to <60; ≥60 to 90 mL/min/1.73 m^2), concomitant tolvaptan use (yes, no), and screening urine albumin-to-creatinine ratio ([UACR], ≤300 mg/g, >300 mg/g). Patients randomized to placebo remained on placebo throughout the study, including undergoing a sham dose

titration. Patients with eGFR ≥60 to 90 mL/min/1.73 m^2 at screening did not comprise more than approximately 40% of enrolled patients.

The maximum bardoxolone methyl dose was determined by baseline proteinuria status. Patients with baseline UACR ≤300 mg/g were titrated to a maximum dose of bardoxolone methyl 20 mg once daily (QD), and patients with baseline UACR >300 mg/g were titrated to a maximum dose of 30 mg QD. Patients receiving bardoxolone methyl started with QD dosing at 5 mg and dose escalated to QD dosing at 10 mg at Week 2, 20 mg at Week 4, and then 30 mg at Week 6 (only if baseline UACR >300 mg/g) unless contraindicated clinically and approved by the Medical Monitor. Dose de-escalation was permitted during the study if indicated clinically, and subsequent dose re-escalation was also permitted to meet the dosing objective of the highest tolerated dose.

From Day 1 forward, all patients in the study followed the same visit and assessment schedule, as described in detail in the Schedule of Assessments. Following randomization on Day 1, patients were scheduled to be assessed in person at Weeks 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, and 100 and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients were to continue study drug treatment through Week 100. Patients were also scheduled to be assessed after the end of treatment at in-person follow-up visits at Weeks 103, 104, 108, and 112.

Efficacy endpoints were to be analyzed after all enrolled patients completed the study and the database was locked. All enrolled patients were scheduled to remain on their blinded treatment assignment through Week 100, and to complete all assessments through Week 112.

Number of Patients (Planned and Analyzed):

Approximately 850 patients were planned to be enrolled in the study. At study termination, a total of 666 patients were enrolled in Study 402-C-1808. 247 patients received at least 1 dose of bardoxolone methyl after Week 52. There were 269 (80.3%) patients receiving bardoxolone methyl who completed treatment or follow-up through Week 52, and 138 (41.2%) were still receiving bardoxolone methyl treatment when the study was terminated.

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

Bardoxolone methyl was supplied in 5-mg, 10-mg, 20-mg, and 30-mg capsules as spray dried dispersion formulation and was administered orally. Batch numbers are provided in Listing 16.1.6.

Duration of Treatment:

All patients were instructed to discontinue treatment with bardoxolone methyl as of 10 May 2023, the study drug termination date.

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

Placebo was administered orally through Week 100.

Criteria for Evaluation:

Efficacy:

Because the study was terminated early, efficacy could not be formally assessed. Summaries of primary and secondary efficacy endpoint data are provided for the primary endpoint of off-treatment change from baseline in eGFR at Week 108 and for the secondary endpoint of change from baseline in eGFR at Week 100.

Safety:

Safety was assessed from reported adverse events (AEs), including serious adverse events; results of standard chemistry, hematology, and urinalysis panels and microscopy; and results of vital sign measurements (including body weight), electrocardiogram, and kidney pain assessments. Additionally, the following laboratory tests were evaluated: eGFR, UACR, N-terminal pro-brain natriuretic peptide, and B-type natriuretic peptide.

Statistical methods:

Subsequent to the decision to terminate bardoxolone methyl clinical development on 10 May 2023 and prior to final database lock (database lock dated 02 October 2023), the final statistical analysis plan (version 3.0, dated 27 July 2023) was approved.

SUMMARY – CONCLUSIONS

- The coronavirus disease 2019 (COVID-19) pandemic had minimal impact on the study. Overall, study medication was interrupted for 27 (8.1%) bardoxolone methyl patients and 39 (11.8%) placebo patients due to COVID-19.
- The majority of the reported treatment-emergent adverse events (TEAEs) reported during the study were mild or moderate in severity. A total of 24 (7.2%) patients in the bardoxolone methyl group and 9 (2.7%) patients in the placebo group had study drug withdrawn due to TEAEs.
- Treatment-emergent adverse events were reported for 314/335 (93.7%) patients. Common TEAEs (>10% of patients) for those treated with bardoxolone methyl group were Muscle spasms (49.0%, 164 patients), Corona virus infection (23.0%, 77 patients), Alanine aminotransferase (ALT) increased (22.7%, 76 patients), Headache (16.4%, 55 patients), Nausea (14.6%, 49 patients), Hepatic enzyme increased (14.3%, 48 patients), Aspartate aminotransferase (AST) increased (14.0%, 47 patients), Fatigue (14.0%, 47 patients), Flank pain (12.8%, 43 patients), Back pain (11.6%, 39 patients), Constipation (11.6%, 39 patients), Nasopharyngitis (11.6%, 39 patients), Arthralgia (10.4%, 35 patients), and Diarrhoea (10.4%, 35 patients). A total of 5 related serious adverse events (SAEs) were reported in 4 patients treated with bardoxolone methyl.
- One fatal outcome occurred in the bardoxolone methyl group (Avalanche accident) and was considered not related to the study treatment by the investigator. Overall, a total of 64 patients reported treatment-emergent SAEs, of which 5 were considered related in patients treated with bardoxolone methyl group and 2 were considered related in patients receiving placebo. No SAEs of end-stage kidney disease were reported.
- Muscle spasms were mostly mild to moderate in severity, with 9 patients treated with bardoxolone methyl assessed as having severe events.
- Overall changes from the current study baseline in most chemistry, hematology, and urinalysis laboratory values appeared to be small and not clinically meaningful.
- Changes in select clinical chemistry parameters of interest, including N-terminal prohormone B-type natriuretic peptide, B-type natriuretic peptide (BNP), ALT, AST, gamma-glutamyl transferase (GGT), bilirubin, magnesium, and UACR as well as vital signs were generally consistent with those seen in prior clinical studies with bardoxolone methyl, including Study 402-C-1603 Phase 2 and Phase 3.

- Blood pressure was well-controlled during the study. Patients in both analysis groups had initial mean decreases from baseline in systolic blood pressure which generally stabilized over time. Overall, mean decreases in body weight and body mass index were observed with bardoxolone methyl treatment and were more substantial than the placebo group.
- Overall mean increases from baseline in eGFR were observed with bardoxolone methyl.
- Although patients treated with bardoxolone methyl experienced increases in BNP, mean BNP values were <100 pg/mL throughout the study for patients in both groups.
- Two patients experienced events of AST increased and ALT increased, which were assessed as severe but were not considered SAEs; treatment was withdrawn for 1 patient and interrupted for the other. Three patients receiving bardoxolone methyl had moderate SAEs of Hepatic enzymes increased (including AST, ALT, and GGT elevations) that resulted in treatment interruptions. All elevations were transient and consistent with the results seen in previous studies with bardoxolone methyl. During the study, there were no TEAEs of Blood bilirubin increased and no >1.5× bilirubin elevations. No Hy's law cases were reported.
- Overall, patients treated with bardoxolone methyl experienced mean decreases in magnesium levels. A total of 19 (5.7%) patients treated with bardoxolone methyl and 5 (1.5%) patients receiving placebo experienced TEAEs of Hypomagnesaemia during the study. Only 1 event in 1 (0.3%) patient in the bardoxolone methyl group was assessed as severe, and none of these events were assessed as SAEs.

Date of the report:
02 February 2024