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Title	Efficacy and safety of the urate-lowering agent febuxostat in chronic heart failure patients with hyperuricemia : results from the LEAF-CHF study
Author(s)	Yokota, Takashi; Kinugawa, Shintaro; Fukushima, Arata et al.
Citation	Heart and vessels, 40, 111-122 https://doi.org/10.1007/s00380-024-02448-9
Issue Date	2024-08-19
Doc URL	https://hdl.handle.net/2115/96009
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature' s AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: https://doi.org/10.1007/s00380-024-02448-9
Type	journal article
File Information	HUSCAP_Manuscript_Heart and Vessels 2024.pdf



Efficacy and safety of the urate-lowering agent febuxostat in chronic heart failure patients with hyperuricemia: results from the LEAF-CHF study

Takashi Yokota^{1,*}, Shintaro Kinugawa^{2,3}, Arata Fukushima¹, Takahiro Okumura⁴,
Toyoaki Murohara⁴, Hiroyuki Tsutsui⁵ on behalf of the LEAF-CHF Investigators

¹Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

²Department Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

³Division of Cardiovascular Medicine, Research Institute of Angiocardiology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

⁴Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

⁵School of Medicine and Graduate School, International University of Health and Welfare, Okawa, Japan

Running title: Febuxostat treatment for chronic heart failure

Word count: 3,996 words

***Correspondence (current address):**

Dr. Takashi Yokota, Institute of Health Science Innovation for Medical Care, Hokkaido University Hospital, Kita-14 Nishi-5, Kita-Ku, Sapporo 060-8648, Japan. Tel.: +81-11-706-6001; Fax: +81-11-706-7613. Email: t-yokota@med.hokudai.ac.jp

Abstract

Hyperuricemia is an independent predictor of mortality in patients with chronic heart failure (CHF). To determine whether febuxostat, a urate-lowering agent, may improve clinical outcomes in CHF patients, we conducted a multicenter, prospective, randomized, open-label, blinded endpoint study with a treatment period of 24 weeks. We randomly assigned Japanese outpatients diagnosed with both CHF with reduced left ventricular ejection fraction (LVEF<40%) and asymptomatic hyperuricemia (serum uric acid [UA] levels >7.0 mg/dl and <10.0 mg/dl) to either a febuxostat group (n=51) or a control group (n=50). The primary efficacy endpoint was the change in log-transformed plasma B-type natriuretic peptide (BNP) levels from baseline to week 24 (or at discontinuation). The secondary efficacy endpoints were the changes in LV systolic or diastolic function evaluated by echocardiography, New York Heart Association (NYHA) class, hemoglobin, and estimated glomerular filtration rate from baseline to week 24, and the change in log-transformed plasma BNP levels or serum UA levels from baseline to weeks 4, 8, 12, 16 and 20 (BNP) or weeks 4, 8, 12, 16, 20 and 24 (serum UA). The primary safety endpoints were occurrence of all-cause death or major cardiovascular events. The mean age of participants was 70 years; 14% were female. The febuxostat group and the control group did not differ with respect to the primary efficacy endpoint ($p=0.13$), although the decrease in log-transformed plasma BNP levels from baseline to each of weeks 4, 8, 12, 16 and 20 was greater in the febuxostat group. There were no significant differences between the two groups in the primary safety endpoints or the secondary efficacy endpoints except reduced serum UA levels in the febuxostat group. Febuxostat did not reduce plasma BNP levels at week 24 in patients with CHF, but it appeared safe with no increase in major cardiovascular events and all-cause or cardiovascular mortality.

Key words: B-type natriuretic peptide, chronic heart failure, clinical trial, oxidative stress, xanthine oxidase inhibitor

Introduction

Hyperuricemia is a common finding in patients with chronic heart failure (CHF) [1].

Growing evidence suggests that hyperuricemia is related to adverse clinical events such as all-cause death and HF hospitalization in patients with CHF [2-4]. In addition, higher serum uric acid (UA) levels are associated with elevated B-type natriuretic peptide (BNP) levels and left ventricular systolic or diastolic dysfunction in these patients [4-6]. Consequently, serum UA has been identified as an independent prognostic biomarker for CHF patients [2, 3, 7].

UA is the end-product of purine metabolism catalyzed by xanthine oxidase (XO), which is known as an important generator of reactive oxygen species (ROS) [8]. We and others have shown that systemic oxidative stress is enhanced in association with disease severity in CHF patients [9-11]. In patients with CHF, XO is highly activated, and increased ROS resulting from XO-catalyzed purine metabolism in the vascular endothelium can cause endothelial dysfunction in the peripheral vessels, leading to increased cardiac afterload [12]. Emerging evidence has drawn attention to the effects of XO inhibitors on clinical outcomes in HF.

Previous studies have shown that allopurinol, a widely used XO inhibitor for patients with hyperuricemia, is likely to have potential benefits in the treatment of

cardiovascular diseases [13]. It has been reported that high-dose allopurinol is associated with reduced risk of all-cause or cardiovascular mortality in CHF patients [14, 15]. In addition, allopurinol treatment is reported to decrease plasma BNP levels in CHF patients [16]. However, in the EXACT-HF trial, allopurinol treatment did not improve clinical status, exercise capacity, quality of life, and left ventricular systolic function in CHF patients with hyperuricemia [17].

Febuxostat, a non-purine-selective inhibitor of XO, is a novel urate-lowering agent for treatment of hyperuricemia and gout. Febuxostat is reported to have greater potency of XO inhibition and a higher urate-lowering effect than allopurinol [18, 19]. In the FREED trial, febuxostat treatment reduced risk of cerebral, cardiovascular, and renal events and all-cause death in elderly patients with hyperuricemia [20] and in those who had a history of cardiovascular diseases [21]. However, it remains unclear whether febuxostat treatment is effective for patients with CHF. We therefore performed a randomized study, called LEAF-CHF (effect of the urate-LowEring Agent Febuxostat in Chronic Heart Failure patients with hyperuricemia), to investigate the efficacy and the safety of febuxostat treatment in hyperuricemic CHF patients with reduced left ventricular ejection fraction (LVEF).

Methods

Study design

We conducted this multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) study to investigate whether febuxostat safely reduces plasma BNP levels in CHF patients with hyperuricemia. The trial design has been published previously [22].

This study was approved by the ethics committee at each participating institution and was registered on UMIN-CTR (no. UMIN000013330). All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

Study patients

Participants were recruited from 38 institutions in Japan. Eligible patients had been diagnosed with CHF (New York Heart Association [NYHA] functional class II or III) with reduced LVEF (<40%) and also asymptomatic hyperuricemia (serum UA levels >7.0 mg/dl and <10.0 mg/dl). Key exclusion criteria were administration of any urate-lowering agent within 2 weeks prior to enrollment. Patients were randomly assigned (in a 1:1 ratio) to either a febuxostat group (febuxostat 10–60 mg once daily plus lifestyle modification) or a control group (lifestyle modification for hyperuricemia) via a web-

based randomization system. The randomization was performed using a minimization method according to the following variables evaluated at enrollment: age (≥ 65 years or not), serum UA (≥ 8.0 mg/dl or not), plasma BNP (≥ 200 pg/ml or not) or NT-proBNP (≥ 900 pg/ml or not), and LVEF ($< 30\%$ or not).

Treatment and assessments

The total study period was 24 weeks, which consisted of an initial 12-week titration period of stepwise dose increase followed by a 12-week dose maintenance period. A 12-week dosing period was chosen based on the previous finding that allopurinol had a BNP-lowering effect at week 12 [16]. The patient presented to his or her hospital every 4 weeks during the treatment period. After randomization, the patients assigned to the febuxostat group received an initial dose of 10 mg daily (Feburic[®] Tablet, Teijin Pharma, Tokyo). Then, the dose was increased to 20 mg daily at week 4, to 40 mg daily at week 8, and to 60 mg daily at week 12, unless the patient's serum UA levels fell below 2.0 mg/dl. The target dose (60 mg daily) of febuxostat was typically maintained until the end of the study. If serum UA levels were < 2.0 mg/dl, the dose was reduced by 20 mg daily from the prior dose. The patients in both groups received guidance for lifestyle modifications (including diet and exercise to reduce serum UA) at baseline and

during the treatment period using a text prepared for this study by the cardiologists.

To ensure objectivity, plasma BNP levels were measured at the central laboratory under blind conditions at baseline and at weeks 4, 8, 12, 16, 20, and 24. Serum high-sensitive C-reactive protein (hs-CRP), plasma oxidized low-density lipoprotein cholesterol (ox-LDL), urinary 8-isoprostanes, and the ratio of urinary albumin to serum creatinine levels were also measured at a central laboratory at baseline and at week 24. In addition, hemoglobin and serum UA were measured at each hospital at baseline and at weeks 4, 8, 12, 16, 20, and 24. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and age using the Japanese equation [23]: $eGFR = 194 \times (\text{serum creatinine, mg/dl})^{-1.094} \times (\text{age, years})^{-0.287} \times (0.739 \text{ if female})$.

Echocardiography was performed at each hospital at baseline and at week 24. To assess LV systolic function, the LVEF was measured by the biplane method of disks. To assess LV diastolic function, we measured the peak early diastolic trans-mitral flow velocity (E) using pulsed-Doppler echocardiography and the peak early diastolic annular velocity (e') at the septal and lateral sides of the annulus with tissue-Doppler imaging. The e' was averaged, and the ratio of E to e' (E/e') was calculated.

We obtained a case report form from the investigators when any events occurred during the study period, irrespective of whether these adverse events were related to

febuxostat treatment.

Efficacy outcomes

The primary efficacy endpoint was the change in log-transformed plasma BNP levels from baseline to week 24. The secondary efficacy endpoints included: (i) the changes in LVEF and E/e' from baseline to week 24, (ii) the changes in NYHA functional class, eGFR, serum UA, and hemoglobin from baseline to each time point (every 4 weeks) until week 24, and (iii) the changes in log-transformed BNP levels from baseline to each time point (every 4 weeks) until week 20. The exploratory endpoints were the changes in (i) log-transformed serum hs-CRP (a systemic inflammation marker), (ii) plasma ox-LDL and urinary 8-isoprostanes (systemic oxidative stress markers), and (iii) the ratio of urinary albumin to serum creatinine levels (a parameter of renal impairment) from baseline to week 24.

Safety outcomes

The primary safety endpoints were the occurrence of all-cause death and major cardiovascular events (i.e., cardiovascular death, hospitalization for worsening HF, hospitalization for other cardiovascular causes, and enhanced HF treatment due to

worsening HF) during the study period. The secondary safety endpoints were any other adverse events that occurred during the study period.

Statistical analysis

The data are presented as means $\pm$ standard deviations (SDs) for continuous variables and as numbers (percentages) for categorical variables. When we compared continuous variables or categorical variables between two groups, we used Student's *t*-test or Fisher's exact test. Based on the intention-to-treat analysis principle, the outcomes were primarily analyzed using a full-analysis set which included all the randomized subjects who had received treatment at least once after randomization; the per-protocol set which met the study protocol was also used for analysis as appropriate.

For between-group comparisons of changes in log-transformed plasma BNP levels from baseline to week 24 (as the primary efficacy endpoint), analysis of covariance (ANCOVA) was performed using baseline dummy variables (including age [≥ 65 years or not], serum UA [≥ 8.0 mg/dl or not], and LVEF [$< 30\%$ or not]) as well as log-transformed plasma BNP levels at baseline as the covariates. If the patient's treatment was discontinued before week 24 after randomization, log-transformed plasma BNP levels measured at the end of the trial were used for primary analysis

instead of those measured at week 24. In addition, to support the primary efficacy endpoint, we compared log-transformed plasma BNP levels at baseline and those at week 24 within each group using the paired *t*-test.

With respect to secondary efficacy endpoints except NYHA class, ANCOVA was performed for between-group comparisons and the paired *t*-test was used for within-group comparisons. Changes in NYHA class from baseline to week 24 were analyzed by the Wilcoxon rank-sum test for between-group comparison and the Wilcoxon signed-rank test for within-group comparison. In addition, the Kaplan-Meier method was used to estimate the event rates throughout the study period for each group, and the log-rank test was used to compare these event rates between groups. A Cox regression analysis was used to estimate relative risk ratios. Relative risks were presented as hazard ratios with 95% confidence intervals (CIs). The same analysis was performed using a per-protocol set to confirm the robustness of the results. Two-sided *p*-values <0.05 were taken to indicate statistical significance. All analyses were performed with the use of SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients

The first patient was enrolled on December 25, 2014. The target sample size to test the hypothesis that febuxostat treatment might reduce plasma BNP levels at week 24 in CHF patients had been initially estimated at 200 patients, as described previously [22]. However, before the target sample size was reached, the Food and Drug Administration (FDA) issued a public safety alert concerning febuxostat for management of hyperuricemia in gout, reporting that febuxostat might increase all-cause and cardiovascular mortality compared to allopurinol [24]. This notice was in response to the results of the CARES trial [25], although there was no significant difference between the febuxostat and allopurinol groups in the primary composite endpoints of cardiovascular events. After this notice, we asked the Independent Data Monitoring Committee whether we could continue our clinical trial. The Committee made the decision that this clinical trial could be continued until the completion of the treatment period of all patients who had already been registered at the time of the decision. However, due to the safety concerns, no further patients were enrolled after the decision. The last patient's follow-up was completed on July 10, 2018.

A total of 108 patients with CHF underwent randomization before December 2017, the time of the FDA notice, but 7 patients who were lost to follow-up before the start of intervention were excluded (**Figure 1**). Of the remaining 101 patients, 51

patients were assigned to the febuxostat group, and 50 patients were assigned to the control group. During the study period, a total of 17 patients (n=6 in the febuxostat group and n=11 in the control group) discontinued the treatment before week 24. The per-protocol analysis was performed in a total of 92 patients (n=47 in the febuxostat group and n=45 in the control group) for whom data were obtained both at baseline and at week 24 (or at discontinuation). The population of the safety-analysis set was the same as that of the full-analysis set.

The baseline characteristics of the participants in the febuxostat group and the control group were shown in **Table 1**. The mean age of the participants was 70 years, and the percentage of females in the total CHF cohort was 14%. Regarding HF etiology, CHF had ischemic cause in 38% of the total cohort, and non-ischemic cause such as dilated cardiomyopathy in the remainder. All patients had HF with reduced LVEF (HFrEF; mean LVEF 29.5%).

At baseline, serum UA levels and plasma BNP levels were comparable between the febuxostat and the control groups (**Table 2**). There were no significant differences in baseline exploratory variables including systemic oxidative stress and inflammation markers (**Table 2**).

Primary and secondary efficacy endpoints

With respect to the primary efficacy endpoint, the change in log-transformed plasma BNP levels from baseline to week 24 (or discontinuation) did not significantly differ between the febuxostat group and the control group, although the decrease in log-transformed plasma BNP levels from baseline to each time point from week 4 to week 20 was significantly greater in the febuxostat group compared to the control group (**Figure 2**). In the within-group comparison, a significant reduction of log-transformed plasma BNP levels was observed at week 24 (or discontinuation) compared to the baseline BNP levels in the febuxostat group ($p<0.01$), but no such significant reduction was observed in the control group ($p=0.09$). In the post-hoc subgroup analysis classified according to achievement of the target dose (i.e., 60 mg daily) of febuxostat at the end of the trial, there was no significant difference in the decrease in log-transformed plasma BNP levels from baseline to week 24 between the febuxostat and the control groups, irrespectively of achievement of the target dose (**Supplementary Figure S1**). Similarly, there was no significant difference in the decrease in log-transformed plasma BNP levels from baseline to week 24 between the febuxostat group and the control group even after the total CHF patient cohort was divided into the ischemic and the non-ischemic CHF patient cohorts (**Supplementary Figure S2**).

There was no significant difference in the changes in LVEF, E/e', eGFR, and hemoglobin levels from baseline to week 24 (or discontinuation) between the groups, although a significant increase in LVEF was observed in both groups in the within-group comparison (**Table 3**). The change in NYHA functional class from baseline to each of weeks 4, 8, 12, 16, 20, and 24 did not differ between the febuxostat and the control groups (data not shown). As expected, the decrease in serum UA levels from baseline to each of weeks 4, 8, 12, 16, 20, and 24 after intervention was significantly larger in the febuxostat group compared to the control group (**Figure 3**). Because of the strong urate-lowering effect of febuxostat, 8 patients (16%) in the febuxostat group experienced hypouricemia with a serum UA level <2.0 mg/dl at least once during the study period.

Exploratory endpoints

There were no significant differences in the changes in log-transformed serum hs-CRP, plasma ox-LDL, urinary 8-isoprostanes, or the ratio of urinary albumin to serum creatinine levels from baseline to week 24 (or discontinuation) between the groups (**Table 4**).

Primary and secondary safety endpoints

During the study period, there was no all-cause death in either group (**Table 5**). With respect to major cardiovascular events, 7 patients (14%) in the febuxostat group and 5 patients (10%) in the control group were hospitalized due to worsening HF or other cardiovascular causes, but there was no statistical significance in the numbers of these events between groups (**Table 5**). In addition, the number of patients whose treatment was enhanced due to worsening HF at the outpatient ward during the study period was 4 (8%) in the febuxostat group and 5 (11%) in the control group, with no significant difference between them (**Table 5**). With respect to any other adverse events (i.e., secondary safety outcomes), there was no statistical significance in the incidence rates of each event type between groups (**Table 6**).

Discussion

In this multicenter randomized trial involving hyperuricemic CHF patients with a reduced LVEF, febuxostat treatment decreased plasma BNP levels at all time points from week 4 to week 20, but this beneficial effect of febuxostat was diminished at week 24 when compared to the control group despite a significant reduction of serum UA levels by febuxostat. Notably, 24-week febuxostat treatment did not increase serious

adverse events including all-cause or cardiovascular mortality in this population.

To our knowledge, this is the first study to examine whether febuxostat treatment has a BNP-lowering effect in HFrEF patients with hyperuricemia. In the present study, plasma BNP levels were decreased in the febuxostat group compared to the control group at each time point (every 4 weeks) during a 12-week dose titration period and a subsequent 8-week dose maintenance period, suggesting that febuxostat treatment is effective in hyperuricemic HFrEF patients for at least 20 weeks. Although febuxostat treatment did not reduce plasma BNP levels at week 24, our findings of temporal but potential benefits of febuxostat in HF management may support further exploration of longer-term efficacy and safety of febuxostat in CHF patients.

Febuxostat is expected to have a cardioprotective effect against oxidative stress and inflammation via selective inhibition of XO [26]. Although febuxostat significantly reduced serum UA levels during the study period, it did not improve markers of systemic oxidative stress and inflammation in our population. Accordingly, we could not elucidate the mechanism by which febuxostat decreased patients' plasma BNP levels at each time point until week 20. One hypothesis is that febuxostat might decrease the afterload with improved endothelial function via suppression of endothelium-bound XO activity, because elevated activity of endothelial-bound XO is related to endothelial

dysfunction in CHF patients [12].

In the present study, febuxostat treatment did not achieve a significant reduction in plasma BNP levels at week 24 compared to the control treatment. There are several possible reasons for this negative result of the primary efficacy endpoint. First, the total number of patients in our cohort was only roughly half the target sample size, which might have led to lower statistical power. Second, 17% of participants discontinued treatment before the end of study period; however, even when these patients were excluded, the result of the primary efficacy endpoint did not change. Third, the dose of febuxostat might have been insufficient to reduce plasma BNP levels in patients with CHF. It has been reported that febuxostat has a dose-dependent UA-lowering effect in patients with hyperuricemia [27, 28]. In the present study, the percentage of CHF patients who reached the target dose of febuxostat at week 12 (at the end of titration period) was 52.3%, but that percentage was decreased to 34.1% at week 24 and 16.7% at discontinuation of follow-up (**Figure 4**). In some cases, the attending cardiologist chose to reduce the febuxostat dose for some reason (including minor adverse events) other than hypouricemia with serum UA levels <2.0 mg/dl. Finally, in the control group, plasma BNP levels at week 24 tended to be lower than baseline BNP levels, which might diminish between-group difference in the changes in log-transformed plasma

BNP levels from baseline to week 24. One possible reason might be lifestyle change, but unfortunately, we did not monitor participant's food intake and physical activity during the study period.

In the present study, HFrEF patients with serum UA levels ≥ 10 mg/dl were not included, considering possible needs of urate-lowering agents during follow-up. In the PARADIGM-HF trial, elevated serum UA levels were an independent predictor of hospitalization and mortality in HFrEF patients, which was more apparent in those with serum UA levels ≥ 8.6 mg/dl [29]. In the OPT-HF trial which included HFrEF patients, oxypurinol, an active metabolite of allopurinol, did not improve clinical status in the entire patient cohort, but post-hoc subgroup analysis suggested potential benefits in those with serum UA levels ≥ 9.5 mg/dl [30]. On the contrary, the EXACT-HF trial showed that high-dose allopurinol did not improve clinical outcomes despite marked reduction of serum UA in HFrEF patients with serum UA levels ≥ 9.5 mg/dl [17]. Taken together, it is still controversial whether highly elevated baseline UA levels might influence effects of urate-lowering agents on clinical outcomes in HFrEF patients.

In the CARES trial, the rate of all-cause and cardiovascular mortality was higher in patients with combined gout and cardiovascular diseases among those using febuxostat than those using allopurinol [25]; this triggered the FDA's public safety alert

concerning the cardiovascular risk of febuxostat [24]. However, the high rates of discontinuation and loss to follow-up raised questions about the validity of the findings in the CARES trial [31]. Indeed, the CARES sub-analysis revealed increased risk of cardiovascular mortality in the initial stage after discontinuation of febuxostat or allopurinol [32]. In addition, subsequent studies have shown inconsistent outcomes [26]. A large randomized clinical trial conducted in Europe (the FAST trial) showed that febuxostat was non-inferior to allopurinol with respect to incidence of major cardiovascular events in patients with gout, and that long-term use of febuxostat is not associated with increased risk of all-cause and cardiovascular death [33]. Until now, the exact effect of febuxostat on cardiovascular risk has not been clearly proved, and the mechanisms underlying the differences in findings between febuxostat and allopurinol remain unsolved [26]. More evidence is needed to determine the cardiovascular risk, if any, of febuxostat and to expand the potentially beneficial clinical use of urate-lowering therapy in patients with CHF.

In the present study, 16% of the CHF patients who were treated with febuxostat were temporarily experienced hypouricemia with a serum UA level <2.0 mg/dl, and thus, the dose of febuxostat had to be reduced in these patients. Given that febuxostat has a dose-dependent UA-lowering effect, serum UA levels should be carefully

monitored to avoid hypouricemia especially in patients who receive high dose of febuxostat.

Several limitations should be noted. First, the patient cohort was smaller than we had expected. Second, the rate of female patients in our CHF patient cohort was smaller than that in general CHF population. Third, the rate of patients with mild CHF (i.e., NYHA functional class II) was much higher than the rate of those with moderate to severe CHF (i.e., NYHA functional class III), which might have weakened the BNP-lowering effect of febuxostat. Fourth, this was an open-label study, which might have influenced the cardiologists' choice of care during follow-up. To minimize this influence, plasma BNP levels were measured at a central laboratory under blind conditions, but we could not completely eliminate potential influence of treatment bias. Finally, we did not evaluate other possible efficacy outcomes such as exercise capacity and quality of life. Further studies are needed to investigate effects of febuxostat on other outcomes in CHF patients.

Conclusions

In this prospective, randomized, open-label trial, the change in log-transformed plasma BNP levels from baseline to week 24 did not differ significantly between the febuxostat

group and the control group in CHF patients with reduced LVEF showing asymptomatic hyperuricemia. Notably, febuxostat treatment did not increase the occurrence of major adverse events including all-cause and cardiovascular mortality during 24-week follow-up in this population.

Acknowledgements

We thank the LEAF-CHF study participants, investigators, medical staff, and clinical research coordinators who contributed to this study.

Funding

This study was supported by grants from Teijin Pharma Ltd.

Conflict of interest

This study was designed by the authors in collaboration with Teijin Pharma Ltd. and the contract research organization (Hubitgenomix Co., Tokyo), but Teijin Pharma Ltd. had no involvement in data collection, event evaluation, or data analysis. This study was supported by Hubitgenomix Co., and the first manuscript was written by Go Ichien, Naoto Minagawa, and Yasuhiko Koezuka (Hubitgenomix Co.). The manuscript was reviewed and revised by all the authors, and all authors approved the final manuscript.

H.T. has received lecture fees and donations from Teijin Pharma Ltd. The other authors declare no conflicts of interest relevant to this study.

Appendix

Participating institutions: Kyusyu University Hospital, Hokkaido University Hospital, Nagoya University Hospital, Tokyo Medical and Dental University, Okayama University Hospital, Kitasato University Hospital, The University of Tokyo Hospital, Nara Medical University Hospital, Osaka University Hospital, Tohoku University Hospital, Hyogo College of Medicine, Jichi Medical University Saitama Medical Center, Yamaguchi University Hospital, Tottori University Hospital, The Jikei University School of Medicine, Sapporo Medical University Hospital, Heartsounds Mori Clinic, Tosei General Hospital, Nishio Municipal Hospital, Osaka General Medical Center, Sakurabashi Watanabe Hospital, National Cerebral and Cardiovascular Center, Sakakibara Heart Institute, Toranomon Hospital, St. Marianna University School of Medicine, Nagoya City University Hospital, Hiroshima University, Sanin Rosai Hospital, National Defense Medical College Hospital, Osaka Medical College Hospital, Medical Corporation JR Hiroshima Hospital, Masao Fujii Memorial Hospital, Hiroshima Prefectural Hospital, Otaru Kyokai Hospital, Showa University Hospital, Sapporo City General Hospital, Tokuyama Central Hospital, Graduate School of Medicine and Faculty of Medicine Kyoto University.

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Table 1. Baseline characteristics of CHF patients

	Febuxostat (n=51)	Control (n=50)
Age (years)	70 ± 13	69 ± 12
Female	6 (12%)	8 (16%)
Weight (kg) ^a	57.7 ± 11.1	60.5 ± 12.0
BMI (kg/m ²) ^a	22.3 ± 3.3	22.7 ± 3.8
NYHA class:		
II	41 (80%)	38 (76%)
III	10 (20%)	12 (24%)
Primary cause of HF:		
Ischemic	19 (37%)	19 (38%)
Non-ischemic	32 (63%)	31 (62%)
Echocardiography:		
LVEF (%)	30.0 ± 7.0	29.0 ± 6.8
E/e' ^b	15.5 ± 7.6	14.6 ± 11.1
Comorbidities:		
Hypertension	25 (49%)	24 (48%)
Diabetes	17 (33%)	17 (34%)
Dyslipidemia	22 (43%)	33 (66%)
Atrial fibrillation	11 (22%)	15 (30%)
HF therapies:		
ACE inhibitor or ARB	43 (84%)	43 (86%)
β-blocker	49 (96%)	40 (80%)
MRA	38 (75%)	36 (72%)
ICD	2 (4%)	2 (4%)
CRT or CRT-D	10 (20%)	9 (18%)

Data are means ± standard deviations or n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-D, CRT defibrillator; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association. a) Body weight and BMI were available for 100 patients (n=50 in the febuxostat group; n=50 in the control group). b) The E/e' value was available for 78 patients (n=37 in the febuxostat group; n=41 in the control group).

Table 2. Laboratory and exploratory variables data at baseline in CHF patients

	Febuxostat (n=51)	Control (n=50)	p-value
Laboratory data:			
Hemoglobin (g/dl)	13.4 ± 1.5	13.4 ± 2.4	0.90
Serum uric acid (mg/dl)	8.0 ± 0.8	8.3 ± 0.8	0.12
eGFR (ml/min/1.73 m ²)	54.0 ± 15.3	51.9 ± 12.1	0.45
Plasma BNP (pg/ml) ^a	414.8 ± 253.9	367.2 ± 304.9	0.15
Exploratory variables:			
Serum hs-CRP (ng/ml) ^a	1781 ± 3455	2340 ± 3632	0.19
Plasma ox-LDL (U/l) ^a	97.9 ± 35.4	104.9 ± 41.8	0.37
Urinary 8-isoprostanes/Cr (pg/mg Cr) ^b	283.2 ± 111.8	296.5 ± 176.0	0.66
Urinary albumin Cr ratio (mg/gCr) ^b	91.4 ± 343.0	40.7 ± 106.5	0.33

Data are means ± standard deviations. BNP, B-type natriuretic peptide; Cr, creatinine; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitive C-reactive protein; ox-LDL, oxidized low density lipoprotein cholesterol. a) Plasma BNP, serum hs-CRP and plasma ox-LDL levels were available for 99 patients (n=50 in the febuxostat group; n=49 in the control group). b) Urinary 8-isoprostanes/Cr and albumin Cr ratio were available for 98 patients (n=49 in the febuxostat group; n=49 in the control group).

Table 3. Changes in echocardiographic and laboratory data from baseline to week 24 (or discontinuation) in CHF patients

	Febuxostat (n=50)	Control (n=48)	p-value
LVEF (%) ^a	2.19 (0.01 to 4.37)*	3.16 (1.01 to 5.32)*	0.53
E/e' ^b	-0.37 (-3.19 to 2.45)	-0.13 (-2.81 to 2.55)	0.90
Hemoglobin (g/dl)	-0.11 (-0.41 to 0.19)	0.04 (-0.27 to 0.34)	0.51
eGFR (ml/min/1.73 m ²)	-0.12 (-3.02 to 2.78)	-1.38 (-4.34 to 1.58)	0.55

Data are least-squared means (95% confidence intervals). * $p < 0.05$ baseline vs. week 24 (or discontinuation) within each group. Abbreviations are as shown in Tables 1 and 2. The analysis of covariance was performed using each baseline echocardiographic or laboratory data point as the covariate for between-group comparison, and the paired t -test was performed for within-group comparison. a) The value of LVEF was available for 85 patients (n=42 in the febuxostat group; n=43 in the control group). b) The value of E/e' was available for 59 patients (n=28 in the febuxostat group; n=31 in the control group).

Table 4. Changes in exploratory endpoints from baseline to week 24 (or discontinuation) in CHF patients

	Febuxostat (n=46)	Control (n=45)	p-value
Log-transformed serum hs-CRP	0.020 (-0.127 to 0.167)	0.099 (-0.050 to 0.248)	0.46
Plasma ox-LDL (U/l)	-1.1 (-9.8 to 7.6)	-2.3 (-11.2 to 6.5)	0.84
Urinary 8-isoprostanes/Cr (pg/mg Cr) ^a	4.4 (-38.6 to 47.4)	14.2 (-29.3 to 57.7)	0.75
Urinary albumin Cr ratio (mg/gCr) ^a	-20.5 (-52.5 to 11.6)	-13.2 (-45.6 to 19.2)	0.75

Data are least-squared means (95% confidence intervals). Abbreviations are as shown in Table 2. The analysis of covariance was performed using each baseline exploratory variable as the covariate for between-group comparison. a) Urinary 8-isoprostanes/Cr and albumin Cr ratio were available for 89 patients (n=45 in the febuxostat group; n=44 in the control group).

Table 5. Major adverse events during the study period

	Febuxostat (n=51)	Control (n=50)	Log-rank test	Cox regression	
				Hazard ratio (95% CI)	p-value
All-cause death	0 (0%)	0 (0%)	–	–	–
Cardiovascular death	0 (0%)	0 (0%)	–	–	–
Hospitalization for worsening HF	6 (12%)	3 (7%)	0.33	1.97 (0.49–7.88)	0.34
Hospitalization for other cardiovascular causes	1 (2%)	2 (5%)	0.49	0.44 (0.04–4.85)	0.50
Enhanced HF treatment due to worsening HF	4 (8%)	5 (11%)	0.67	0.75 (0.20–2.80)	0.67

Data are number (%) of events. CI, confidence interval.

Table 6. Other adverse events during the study period

	Febuxostat (n=51)	Control (n=50)	p-value
Anemia progression	1 (2%)	0 (0%)	1.00
Anorexia	1 (2%)	0 (0%)	1.00
Cholecystitis	0 (0%)	1 (2%)	0.50
Coronary artery stenosis	1 (2%)	0 (0%)	1.00
Cough	1 (2%)	0 (0%)	1.00
Decreased platelets	0 (0%)	1 (2%)	0.50
Dehydration	0 (0%)	2 (4%)	0.24
Dizziness	1 (2%)	0 (0%)	1.00
Dyspnea	0 (0%)	1 (2%)	0.50
Fatigue	3 (6%)	1 (2%)	0.62
Herpes zoster	0 (0%)	1 (2%)	0.50
Hyperkalemia	0 (0%)	1 (2%)	0.50
Increased alanine transaminase	1 (2%)	0 (0%)	1.00
Increased aspartate transaminase	1 (2%)	0 (0%)	1.00
Increased serum creatinine	0 (0%)	1 (2%)	0.50
Increased total bilirubin	1 (2%)	0 (0%)	1.00
Increased triglycerides	1 (2%)	0 (0%)	1.00
Influenza	0 (0%)	2 (4%)	0.24
Light headedness	0 (0%)	1 (2%)	0.50
Overactive bladder	1 (2%)	0 (0%)	1.00
Orthostatic hypotension	0 (0%)	1 (2%)	0.50
Palpitation	0 (0%)	1 (2%)	0.50
Pancreatitis	0 (0%)	1 (2%)	0.50
Paroxysmal atrial flutter	0 (0%)	1 (2%)	0.50
Persistent cough	1 (2%)	0 (0%)	1.00
Reduced blood pressure	0 (0%)	1 (2%)	0.50
Stomachache	0 (0%)	1 (2%)	0.50
Subdural hematoma	0 (0%)	1 (2%)	0.50
Ventricular tachycardia	0 (0%)	1 (2%)	0.50
Worsening renal function	0 (0%)	1 (2%)	0.50

Data are number (%) of events.

Figure legends

Fig. 1: Enrollment, randomization, treatment, and analytic sample.

Fig. 2: Changes in log-transformed plasma BNP levels from baseline to each time point in CHF patients. Data are least-squared means (95% confidence intervals). * $p < 0.05$ vs. the control group at each time point. For between-group comparisons, the analysis of covariance was performed using baseline dummy variables (including age [≥ 65 years or not], serum UA [≥ 8.0 mg/dl or not], and LVEF [$< 30\%$ or not]) as well as log-transformed plasma BNP levels at baseline as the covariates. BNP, B-type natriuretic peptide; D, discontinuation.

Fig. 3: Changes in serum uric acid levels from baseline to each time point in CHF patients. Data are least-squared means (95% confidence interval). * $p < 0.01$ vs. the control group at each time point. For between-group comparisons, the analysis of covariance was performed using baseline serum UA levels as the covariate. D, discontinuation.

Fig. 4: Distribution of daily dose of febuxostat during the study period. Data are

percentages of patients in the febuxostat group at each time point.

Figure 1

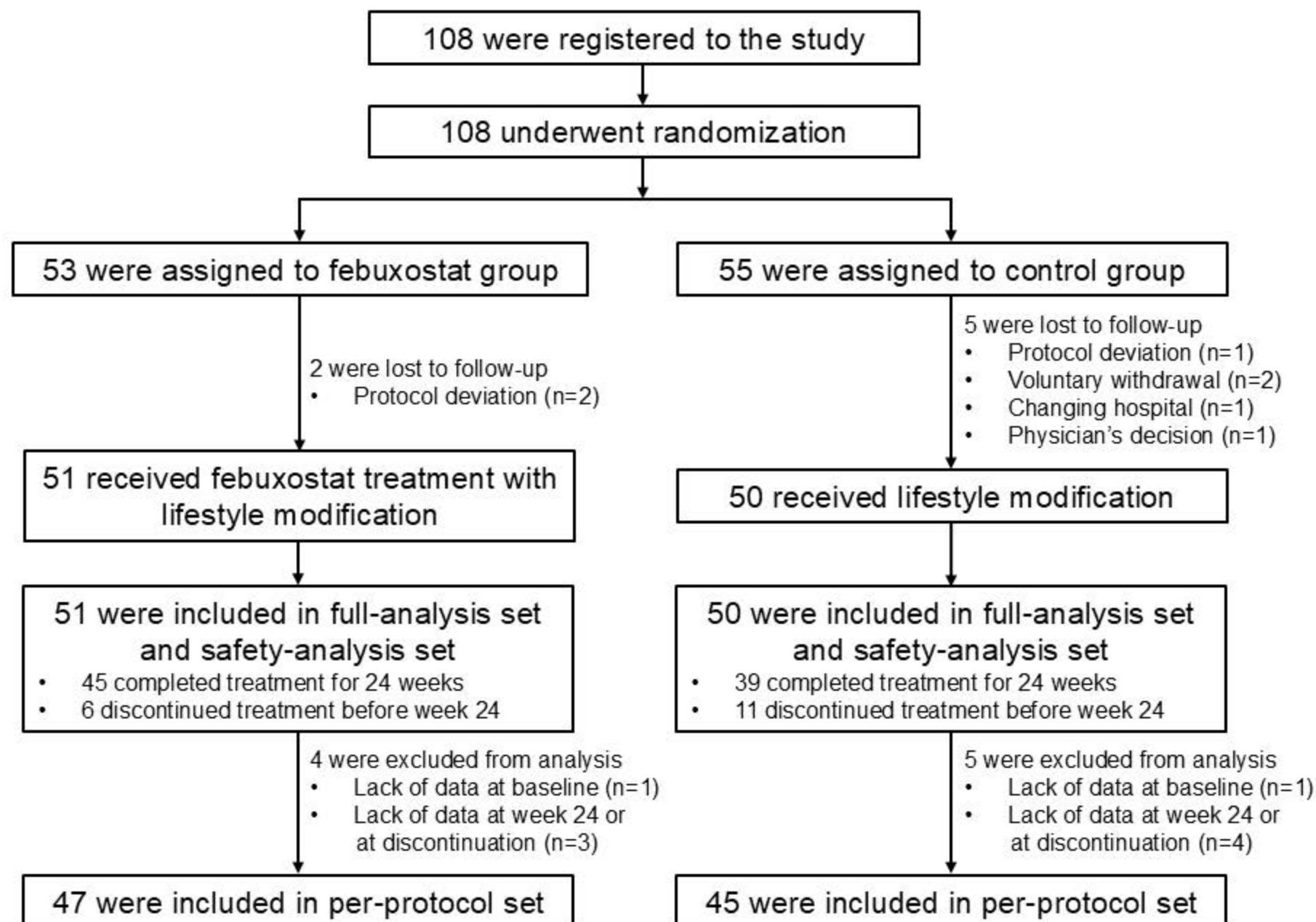


Figure 2

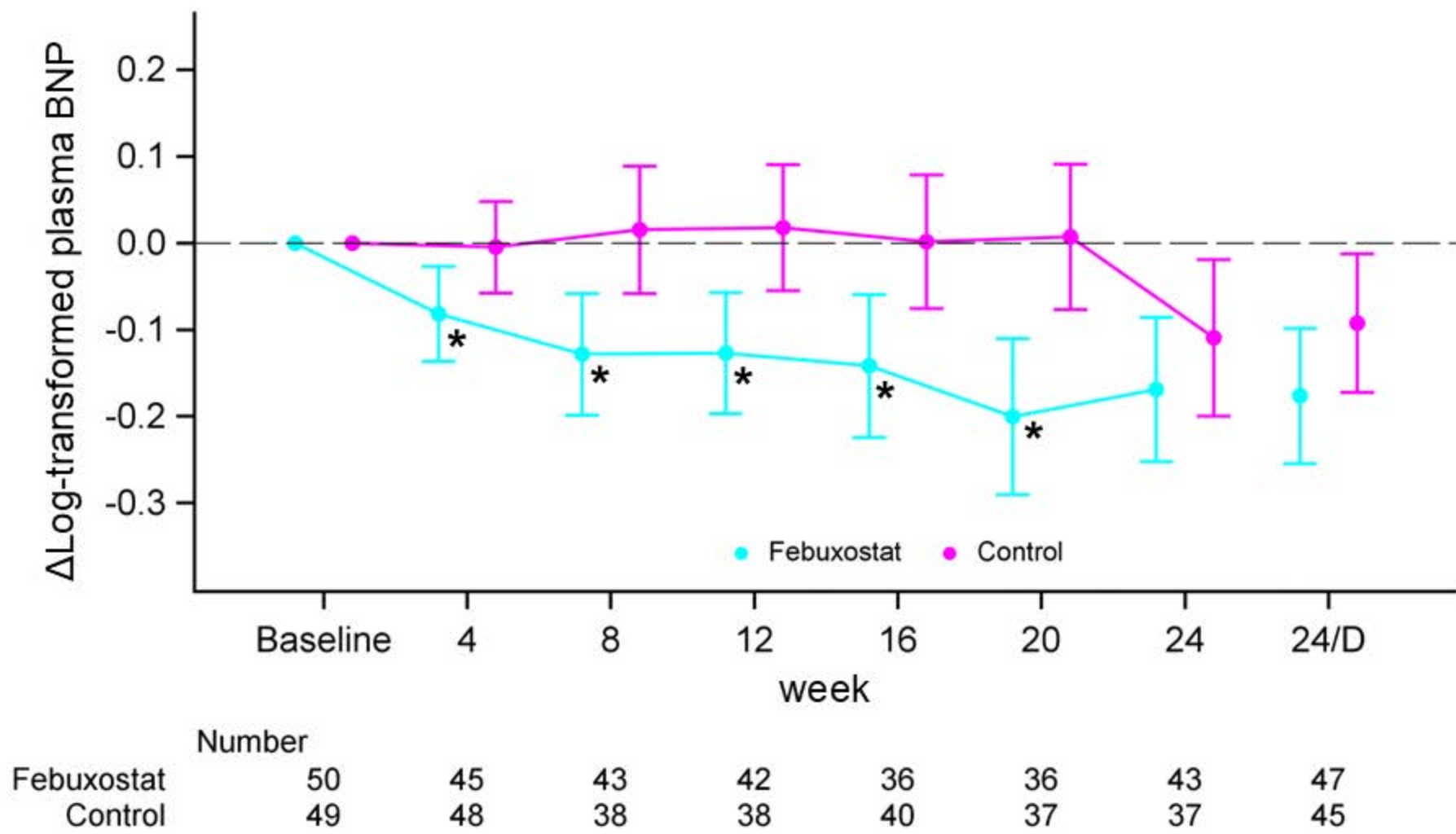


Figure 3

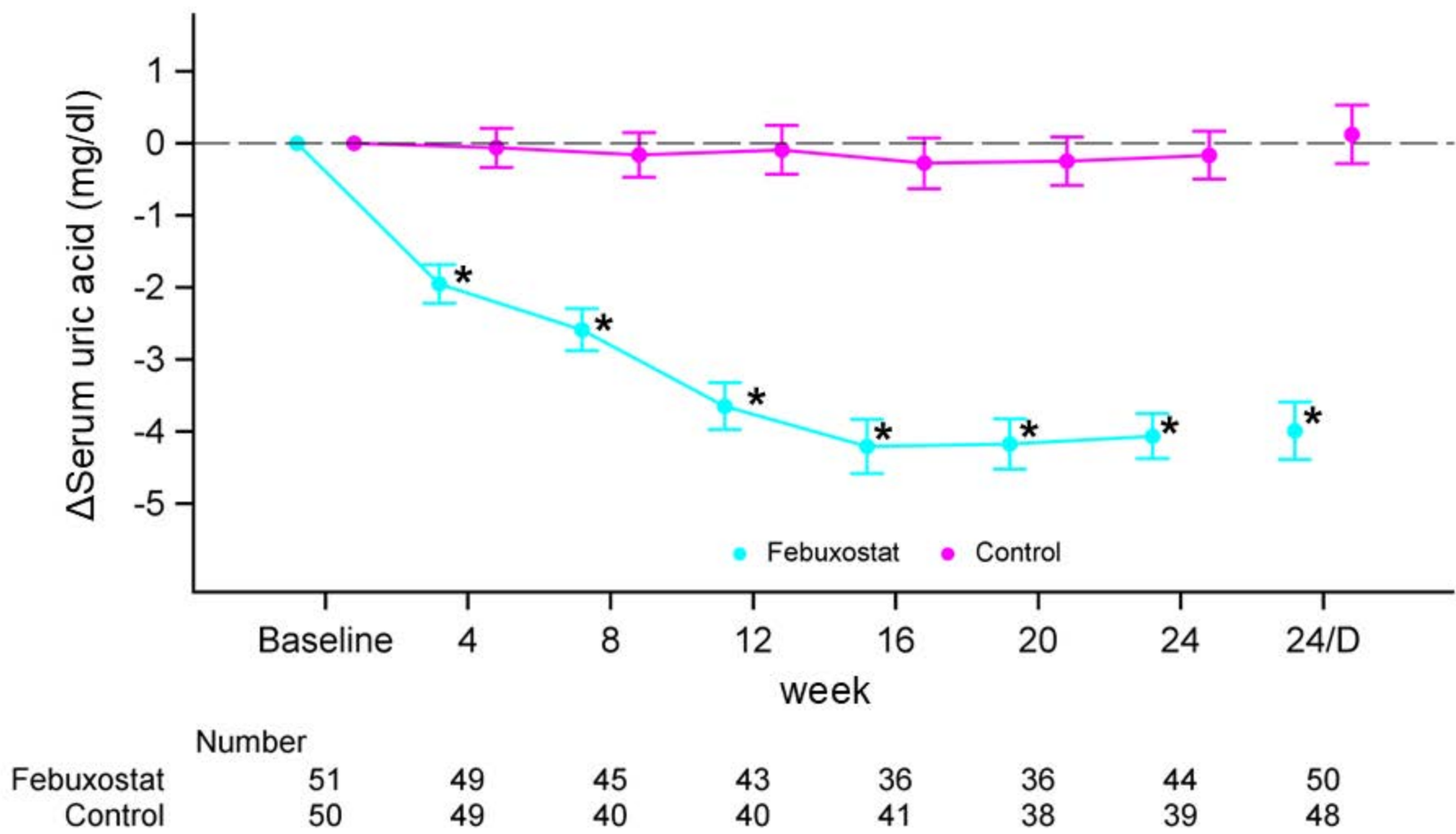


Figure 4

