



Title: A Multicenter, Randomized, Active-Control, Phase 3B Study to Evaluate the Cardiovascular Safety of Febuxostat and Allopurinol in Subjects With Gout and Cardiovascular Comorbidities

NCT Number: NCT01101035

Protocol Approve Date: 27 August 2013

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PROTOCOL AMENDMENT

A Multicenter, Randomized, Active-Control, Phase 3B Study to Evaluate the Cardiovascular Safety of Febuxostat and Allopurinol in Subjects With Gout and Cardiovascular Comorbidities

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015, United States

Study Number: TMX-67_301

IND Number: 58,229 **EudraCT Number:** N/A

Compound: Febuxostat

Date: 27 August 2013 **Amendment Number:** 6

Amendment History:

Date	Amendment Number	Amendment Type	Region
24 August 2009	Initial Protocol	Not applicable	North America
20 January 2010	1	Substantial	North America
24 February 2010	2	Substantial	North America
24 January 2011	3	Substantial	North America
19 May 2011	4	Not Substantial	Canada
26 September 2011	5	Substantial	Global
27 August 2013	6	Substantial	Global

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Issue

Serious adverse event reporting

Medical monitor
(medical advice on
protocol, compound
and medical
management of
subjects)

Responsible medical
officer (carries overall
responsibility for
conduct of study)

PPD



1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

PPD	Date	PPD	Date
PPD	Date	PPD	Date
PPD	Date		

1.3 Protocol Amendment TMX-67_301 Summary of Changes

This document describes changes in reference to Protocol TMX-67_301 Amendment 6, dated 27 August 2013.

Change in Protocol	Rationale
Increased maximum study duration estimate to 9 years.	Slower than expected enrollment duration has extended the overall length of the study.
Exclude non-serious potential cardiovascular events from endpoint adjudication.	Non-serious adverse events are not likely to be adjudicated to a major adverse cardiac events (MACE) endpoint and the Food and Drug Administration (FDA) agreed to remove the requirement for adjudication of non-serious events.
Update visit name to End of Study/Discontinuation of Treatment/Early Termination.	Correction to remove reference to a final Month 60; clarifies the purpose and procedures conducted at this visit type.
Revisions and clarifications in Sections 7.4 and 7.5 for subjects discontinuing study drug treatment with continued participation via follow-up contacts, and subjects early terminating from both study drug and study visits.	Update to section titles and section content revisions more accurately reflects the protocol for subjects with these statuses. Revisions also clarify instances where subjects are no longer followed via follow-up contacts, expectations for attempted contacts with subjects who are lost to follow-up, and instances where subjects are early terminated due to adverse events (AEs).

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Package Insert [14], and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Name of Facility

Location of Facility (City)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015, United States	Compound: Febuxostat	
Title of Protocol: A Multicenter, Randomized, Active-Control, Phase 3B Study to Evaluate the Cardiovascular Safety of Febuxostat and Allopurinol in Subjects with Gout and Cardiovascular Comorbidities	IND No.: 58,229	EudraCT No.: N/A
Study Number: TMX-67_301	Phase: 3B	

Study Design:

This is a phase 3B multicenter, randomized, double-blind, active-controlled study designed to evaluate the cardiovascular (CV) safety of febuxostat compared with allopurinol in subjects with gout and significant CV comorbidities. Approximately 7500 subjects will be randomly assigned to study medication treatment.

The overall duration of the study is dependent on the number of predefined major cardiovascular events (MACE). The length of study is expected to be approximately 9 years. The length of study participation for each subject will vary due to the event driven study design. This study is designed to have a maximum of 624 MACE.

Subjects will be screened at Day -7 for entry. Subjects with cardiovascular comorbidities, gout and (1) a serum urate level (sUA) ≥ 7 mg/dL or (2) with a sUA ≥ 6 mg/dL AND at least 1 flare in the 12 months prior to screening and/or the presence of tophi) and who meet the other selection criteria will be enrolled.

On Study Day 1, eligible subjects will be randomized in a 1:1 ratio to receive either febuxostat once daily (QD) or allopurinol QD. Randomization will be stratified based on baseline renal function: subjects with normal renal function or mild renal impairment (estimated creatinine clearance [eCLcr] ≥ 60 mL/min) versus subjects with moderate renal impairment (eCLcr ≥ 30 but < 60 mL/min).

Subjects randomized to febuxostat will initially receive the 40 mg dose QD. Subjects will remain on 40 mg for the remainder of the study if their sUA is < 6.0 mg/dL at the Week 2 Visit (± 3 days). If their sUA is ≥ 6.0 mg/dL at the Week 2 Visit (± 3 days) they will receive febuxostat 80 mg QD at Week 4 visit (± 3 days), and will remain on this dose for the remainder of the study. No dose adjustment will be made in the febuxostat based on renal function.

Subjects randomized to allopurinol who have normal renal function or mild renal impairment (eCLcr ≥ 60 mL/min) will initially receive allopurinol 300 mg QD with the dose increased in 100 mg increments monthly until either a sUA < 6.0 mg/dL or an allopurinol dose of 600 mg QD is achieved. Subjects randomized to allopurinol who have moderate renal impairment (eCLcr ≥ 30 but < 60 mL/min) will initially receive allopurinol 200 mg QD with the dose increased in 100 mg increments monthly until either a sUA < 6.0 mg/dL or an allopurinol dose of 400 mg QD is achieved.

To maintain the double-blind nature of the study, febuxostat and allopurinol tablets will be over-encapsulated and matching placebo capsules will be manufactured which are identical in appearance. Subjects will orally self administer 2 capsules each morning in the appropriate combination for their assigned dose and treatment. For details regarding the appropriate dose combination, please see Section 8.1.3.

Serum urate levels will be unblinded to the investigator and Takeda through the Week 10 Visit of the study to facilitate dose increases based on sUA response. After the Week 10 Visit, sUA measurements will be blinded to Takeda and the investigator. The interactive voice-activated response system/interactive web-activated response system (IVRS/IWRS) will manage the treatment assignment at randomization and throughout the study medication treatment period.

Subjects currently on urate-lowering therapy (ULT) will discontinue treatment at the Day -7 Screening Visit, and will begin colchicine 0.6 mg QD for gout flare prophylaxis. Subjects not on ULT will begin colchicine 0.6 mg QD on the Day 1/Randomization Visit. All subjects will receive gout flare prophylaxis for the first six months of the study medication treatment period. Alternatively, if colchicine is not tolerated and the subject's eCLcr is ≥ 50 mL/min, they will be administered naproxen 250 mg twice daily (BID) with lansoprazole 15 mg QD. If a subject has been maintained on an appropriate dose (as determined by the investigator) of another proton pump inhibitor (PPI) other than lansoprazole, he/she may continue treatment with it during this study. In instances when subjects should not receive colchicine or naproxen, other nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone may be provided at the investigator's discretion in accordance with the stated guidelines listed under the Excluded Medications and Treatments section of the protocol. In the event that colchicine, naproxen or other NSAIDs, proton pump inhibitors or prednisone are not tolerated or are contraindicated, the Investigator may choose not to use prophylaxis but to manage the subject's gout flares as they occur. Alternatively, if colchicine 0.6 mg daily is not tolerated by the subject, 0.6 mg every other day may be used.

Following the Day 1 Visit, subjects will return for study visits during the first 3 months of the study based on the subject's sUA response. Once a subject sUA < 6.0 mg/dL there will be no further visits until Month 3.

All subjects will return at Week 2 for measurement of sUA and all subjects will return for a Week 4 and Month 3 visit. If the Week 2 sUA level is < 6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Month 3. If the Week 2 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Week 6.

For the subset of subjects who have a Week 6 visit, if the Week 6 sUA level is < 6.0 mg/dL, the subject will be dispensed study medication at Week 8, and the next visit will occur at Month 3. If the Week 6 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 8 and the next visit will occur at Week 10.

For the subset of subjects who have a Week 10 visit, the subject will be dispensed study medication at the Month 3 visit. After the Month 3 visit, no further dose adjustments will be made. All subjects will have a Month 3 and Month 6 visits.

Following the Month 6 visit, all subjects will have visits every 6 months for the duration of the study. In addition, subjects with moderate renal impairment (eCLcr ≥ 30 but < 60 mL/min) and/or subjects who are elderly (≥ 65 years of age) will have visits at Month 9 and Month 15 to monitor the liver function tests (LFTs). Subjects who are withdrawn from study medication treatment but have not withdrawn consent will be contacted every 2 months for the duration of the study or until the subject experiences a CV event that is positively adjudicated as a MACE. A Data Monitoring Committee (DMC) unblinded to treatment assignment will periodically review results obtained in the study, including results at 3 planned interim analyses. They will monitor the progress and the ongoing safety of subjects enrolled into the study. An Independent CV Endpoints Committee will prospectively review all suspected serious CV events using blinded data. All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV SAEs.

Primary Objective:

The objective of this study is to compare the risk of predefined MACE during treatment with febuxostat and allopurinol in subjects with gout and CV comorbidities.

Subject Population:

Male subjects ≥ 50 years of age and female subjects ≥ 55 years of age and at least 2-years post-menopausal with gout and a prior history of major CV or cerebrovascular disease.

Number of Subjects:

Estimated total of 7500 subjects:
3750 subjects randomized to febuxostat
3750 subjects randomized to allopurinol

Number of Sites:

Approximately 465 sites (United States, Canada, and Mexico)

Dose Level(s): Febuxostat 40 mg or 80 mg QD Allopurinol 200 mg to 600 mg QD in 100 mg increments	Route of Administration: Oral
Duration of Treatment: The overall duration of the study is dependent on the number of predefined MACE; however, the maximum length of participation is expected to be approximately 9 years. The length of study participation for each subject will vary (ie, due to the event driven study design).	Period of Evaluation: Up to 7 day screening period Maximum of 9 years treatment duration
Main Criteria for Inclusion: Subject eligibility will be determined on the basis of the criteria listed below: <ul style="list-style-type: none"> • The subject or the subject's legally acceptable representative signs a written, informed consent form prior to the initiation of any study procedures. • Male subjects ≥ 50 years and female subjects ≥ 55 years of age and at least 2-years postmenopausal. • In order to enter the study, subject has a history of CV or cerebrovascular disease including at least ONE of the following: <ul style="list-style-type: none"> – Myocardial infarction (MI). – Hospitalized unstable angina. – Cardiac or cerebral revascularization procedure. – Stroke. – Hospitalized transient ischemic attack (TIA). – Peripheral vascular disease (ankle brachial index ≤ 0.6, revascularization and/or a well-documented history of claudication). – History of diabetes mellitus with evidence of micro- or macrovascular disease (retinopathy, neuropathy, nephropathy, small vessel vascular diseases). • Subject has a history or presence of gout defined as having one or more of the American Rheumatism Association criteria for the diagnosis of gout: <ul style="list-style-type: none"> – A tophus proven to contain urate crystals by chemical or polarized light microscopic means, AND/OR – Characteristic urate crystals in the joint fluid, AND/OR – History of at least 6 of the following clinical, laboratory, and x-ray phenomena: <ul style="list-style-type: none"> • More than 1 attack of acute arthritis. • Maximum inflammation developed within 1 day. • Monoarticular arthritis. • Redness observed over joints. • First metatarsophalangeal joint painful or swollen. • Unilateral first metatarsophalangeal joint attack. • Unilateral tarsal joint attack. • Tophus (proven or suspected). • Hyperuricemia. • Asymmetric swelling within a joint on x-ray. • Subcortical cysts without erosions on x-ray. • Joint fluid culture negative for organisms during attack. 	

- Subjects must have either:
 - a sUA level ≥ 7.0 mg/dL at the Screening Visit **OR**
 - a sUA level ≥ 6.0 mg/dL at the Screening Visit **AND** inadequately controlled gout (≥ 1 flare in the 12 months prior to screening and/or the presence of tophi).

Main Criteria for Exclusion:

- Subject has secondary hyperuricemia (eg, due to myeloproliferative disorder, or organ transplant).
- Subject has a history of xanthinuria.
- The subject has received urate-lowering therapy (ie, febuxostat, allopurinol, probenecid, etc.) or excluded medication less than 7 days prior to Study Day 1/Randomization visit. Subject has a known hypersensitivity to febuxostat or allopurinol or any components of their formulation.
- Subject has active peptic ulcer disease.
- Subject has a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the first dose of study medication.
- Subject had a MI or stroke within 60 days prior to the Screening Visit.
- Subject has alanine aminotransferase and/or aspartate aminotransferase values greater than 2 times the upper limit of normal during the screening period.
- Subject has a significant medical condition and/or conditions that would interfere with the treatment, safety, or compliance with the protocol.
- Subject's estimated eCLcr is < 30 mL/min, where eCLcr is calculated using the Cockcroft and Gault formula based on ideal body weight.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

The time from randomization to the first occurrence of any event in the predefined MACE composite, which includes:

- CV death.
- Nonfatal MI.
- Nonfatal stroke.
- Unstable angina with urgent coronary revascularization.

Secondary Endpoints

- The time from randomization to the first occurrence of any Antiplatelet Trialists' Collaborative (APTC) event, which includes:
 - CV death.
 - Nonfatal MI.
 - Nonfatal stroke.
- The time from randomization to the occurrence of each individual event in the pre-defined MACE composite.

Sample Size Justification:

A total of 7500 subjects (3750 per treatment group) are planned to be enrolled in this study. The sample size will provide at least 90% power to meet a noninferiority margin of 1.3 for the hazard ratio (febuxostat relative to allopurinol) for the primary endpoint assuming a true hazard ratio of 1.0 at a 1-sided 2.5% significance level. For the determination of noninferiority between the febuxostat treatment group and the allopurinol treatment group, the sample size calculation assumed constant proportional hazards and exponential survival curves, annual adjudicated MACE composite rate of 2.8%, maximum length of participation of 5 years, accrual time of 2.5 years and annual drop-out rate of 10%. This study is designed to have a maximum of 624 MACE. These assumptions were used prior to the initiation of the study to calculate the number of subjects to be enrolled in order to obtain the required number of MACE.

Statistical Considerations:

The primary endpoint and all other analyses by treatment group will be analyzed according to the randomized treatment using the Full Analysis Set (FAS). The FAS will consist of all subjects who were randomized and received at least one dose of double-blind study medication. If a subject reports a MACE after treatment discontinuation, then the reported event will be counted toward the treatment to which they were randomized.

Safety Analyses

Assuming constant proportional hazards, the hazard ratio for the primary endpoint will be computed based on febuxostat and allopurinol estimated hazard rates. The febuxostat treatment group will be compared to the allopurinol treatment group to test for non-inferiority in the MACE composite rate using a Cox proportional hazards model with treatment and baseline renal function as factors in the model. Non-inferiority of febuxostat to allopurinol will be declared at an interim analysis or at the final analysis if the current 1-sided upper CI for the hazard ratio (febuxostat versus allopurinol) calculated with critical values obtained using the Lan-DeMets-O'Brien-Fleming alpha spending function, which preserves an overall 1-sided false-rejection rate of 2.5%, is less than 1.3.

Analysis of the secondary and other safety endpoints will be conducted similarly using a Cox proportional hazards model. No adjustments will be made for multiplicity.

Additional analysis on the primary safety endpoint will be performed using Cox-proportional hazards model controlling for the effect of NSAIDs use. The model will include treatment group, baseline renal function, and use of NSAIDs as explanatory variables. A similar analysis will control for the effect of low-dose aspirin use.

Interim Analysis and Criteria for Early Termination.

This study is designed to have a maximum of 624 MACE for assessing non-inferiority of febuxostat relative to allopurinol with regard to cardiovascular risk assuming a true hazard ratio of 1.0 and 90% power. Interim analyses will be conducted when approximately 25%, 50% and 75% of the events have occurred, followed by a final analysis. At each analysis, if the upper one-sided confidence limit of the hazard ratio is less than 1.3, the study will be stopped and the non-inferiority of febuxostat relative to allopurinol with regard to cardiovascular risk will be declared.

Periodically during the course of the study a blinded assessment of the annual adjudicated composite MACE rate will be made. The number of subjects planned to be enrolled in this study was based on an event rate of 2.8%, which was based on limited information. Based on the overall blinded composite MACE rate observed, an assessment will be made to determine whether or not to adjust the number of subjects planned for enrollment.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified below. The identified vendors will perform these activities in full or in partnership with the sponsor.

Activity	US and Canada	Mexico
Site Monitoring	PPD	PPD
Central laboratory		
Data management		
Statistical analysis		
Interactive voice-activated response system		
Clinical supply packaging and distribution		
Clinical supply return		

3.2 Principal Investigator

Takeda Development Center Americas, Inc. (TDC) will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLcr	creatinine clearance
COX-2	cyclooxygenase 2
ct.	count
CV	cardiovascular
CVD	cardiovascular disease
DMC	Data Monitoring Committee
DoT	discontinuation of treatment
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
EoS	end of study
ET	early termination
eCRF	electronic case report form
eCLcr	estimated creatinine clearance
FDA	Food and Drug Administration
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
IBW	ideal body weight
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IVRS/IWRS	interactive voice-activated response system/interactive web-activated response system
LFTs	liver function tests
MACE	major adverse cardiovascular event(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
PE	pulmonary embolism
PTE	pretreatment event

QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
sUA	serum urate level
TIA	transient ischemic attack
×ULN	times the upper limit of normal
ULT	urate-lowering therapy
XO	xanthine oxidase

3.4 Corporate Identification

TDC (Europe)	Takeda Development Centre (Europe) Ltd.
TDC (Americas)	Takeda Development Center, Inc.
TDC	TDC (Americas)
TPC	Takeda Pharmaceutical Company Limited
Takeda	TDC (Asia), TDC (Americas), TDC (Europe), and TPC, collectively

4.0 INTRODUCTION

4.1 Background

Gout affects 3 to 5 million individuals in the United States and is increasing in incidence and prevalence [1-3]. Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including cardiovascular (CV) disease, chronic kidney disease, and metabolic syndrome [4-6]. The underlying metabolic aberration in gout is hyperuricemia, which is defined as an elevation in serum uric acid (sUA) level ≥ 6.8 mg/dL. Hyperuricemia develops into gout when urate crystals are formed from supersaturated body fluids and are deposited in joints, tophi, and parenchymal organs eliciting acute inflammatory responses.

Urate-lowering therapy (ULT) is used to treat hyperuricemia in subjects with gout. The goal of therapy is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid. Using ULT to reduce and maintain sUA levels < 6.0 mg/dL ultimately improves the clinical symptoms of gout by reducing the frequency of gout flares, decreasing size and number of tophi, and improving quality of life. Due to the potential for paradoxical flares caused by urate crystal mobilization, anti-inflammatory agents and/or colchicine are given as prophylaxis with ULT during the first 6 months of treatment [7].

Gout subjects also have a high incidence of comorbidities that may be associated with hyperuricemia, gout, or both. This is supported by a growing body of literature demonstrating that sUA level is an independent predictive factor for cardiovascular disease (CVD) when the effects of other risk factors have been controlled. Several recent studies report an increased risk of CV death, myocardial infarction (MI), and stroke associated with higher sUA levels. For example, the Preventive Cardiology Information System Database Cohort Study, which assessed the prognostic value of sUA in 3098 persons at risk for CVD, found that sUA was an independent predictor of death from all causes; for every 1 mg/dL elevation in sUA level, the risk of death from all cause in subjects at high risk of CVD increased by 39% (hazard ratio 1.39, 95% CI 1.28-1.50) without adjusting for other risk factors. After adjusting for other risk factors, the sUA level remained a predictor of death from all causes (hazard ratio=1.26, 95% CI 1.15-1.38) [8]. In the Framingham Heart study, sUA was not an independent predictor of coronary artery disease in men without gout, but there was a 60% excess incidence of coronary artery disease in men with gout never treated with diuretics [9]. The National Health and Nutrition Examination Survey study reported a direct role for hyperuricemia in CV events and mortality, tying sUA levels to increasing CV mortality. These findings persisted even after adjustments were made for age, sex, race, body mass index, smoking, hypertension, and diabetes [10].

4.1.1 Mechanism of Action

Febuxostat is a potent, nonpurine, selective inhibitor of xanthine oxidase (XO) that exhibits antihyperuricemic activity by reducing the formation of uric acid. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine \rightarrow xanthine \rightarrow uric acid. Both steps in this transformation are catalyzed by XO. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. Unlike febuxostat, administration of allopurinol does

not provide persistent enzyme inhibition and has weaker hypouricemic activity. More importantly, because allopurinol and its metabolites are purine analogs, they also inhibit other enzymes involved in purine and pyrimidine metabolism. In contrast, febuxostat is a selective inhibitor of XO.

4.1.2 Nonclinical Data Summary

Relevant CV related nonclinical data are summarized below.

Febuxostat is a nonpurine, selective inhibitor of XO that inhibits the formation of uric acid from hypoxanthine and xanthine. XO inhibition is not known to cause CV adverse effects.

Nonclinical safety pharmacology and secondary pharmacology studies demonstrated no mechanisms associating febuxostat with CV effects at therapeutic exposures. CV safety pharmacology studies included in vitro electrophysiology investigation on cardiac action potential parameters and ion channels (potassium [human *ether-à-go-go*-related gene], sodium, and calcium), and in vivo studies for hemodynamic and electrocardiogram (ECG) effects in both anesthetized and conscious telemetry-monitored dogs. In addition, the in vitro effects of febuxostat on the hemostatic system, protease generation, and platelet function were explored using human blood. Febuxostat did not significantly inhibit nor augment platelet or coagulation responses and did not have any interactions in vitro with heparin, warfarin, or aspirin.

Furthermore, in a long-term (52-week) toxicology study in dogs, no CV toxicity was observed based on electrocardiographic, organ weight, and histopathological examinations.

Febuxostat was also shown to have no detrimental CV effects in animal CV models. Overall, when studied in 6 different animal models specific for CV diseases, febuxostat had no detrimental CV effect, but rather appeared to have beneficial CV effects. In summary, no biological mechanism was identified to be associated with febuxostat that could cause potential CV adverse effects.

4.2 RATIONALE FOR THE PROPOSED STUDY

The febuxostat Phase 3 randomized controlled studies revealed a small number of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) in subjects treated with febuxostat (0.74 per 100 PY with 95% CI 0.36-1.37) compared to allopurinol (0.60 per 100 PY with 95% CI 0.16-1.53). In the phase 3 clinical program for febuxostat approximately 60% of subjects had 2 or more cardiovascular risk factors (including diabetes, hypertension, hyperlipidemia, obesity, and smoking).

In order to further explore the cardiovascular safety of febuxostat, Takeda has committed to conduct a randomized, controlled trial of adequate size and duration to determine whether the use of febuxostat is associated with a moderate increase in the risk of serious adverse cardiovascular outcomes as compared to allopurinol.

This study will enroll subjects with a high cardiovascular risk profile, characterized by the presence of documented history of any of the following: cerebrovascular, coronary, peripheral vascular disease, or the diagnosis of diabetes with microvascular or macrovascular complications.

This randomized controlled study will attempt to enroll populations of interest including women (5%), elderly (20%) and renally impaired (30%).

The primary endpoint of the study will be a pre-defined composite of major adverse cardiovascular events (MACE). The MACE composite endpoint will include: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalized unstable angina with urgent coronary revascularization.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary objective of this study is to compare the risk of predefined MACE during treatment with febuxostat and allopurinol in subjects with gout and CV comorbidities.

5.2 Endpoints

Primary Endpoint

The time from randomization to the first occurrence of any event in the predefined MACE composite, which include:

- CV death.
- Nonfatal MI.
- Nonfatal stroke.
- Unstable angina with urgent coronary revascularization.

Secondary Endpoints

- The time from randomization to the first occurrence of any Antiplatelet Trialists' Collaborative (APTC) event, which includes:
 - CV death.
 - Nonfatal MI.
 - Nonfatal stroke.
- The time from randomization to the occurrence of each individual event in the pre-defined MACE composite.

Additional Endpoints

- The time from randomization to the first occurrence of any event in the pre-defined MACE composite plus any of the following events:
 - Urgent Cerebral revascularization [nonelective].
 - Hospitalized CHF.
 - Arrhythmias not associated with ischemia.
 - Venous and peripheral arterial thromboembolic events; eg, Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE).
 - Transient Ischemic Attack (TIA).
- Percentage of subjects whose average sUA levels from the end of the first year of treatment to the end of the study are <4.0 mg/dL, ≥4 to <5.0 mg/dL, ≥5 to <6.0 mg/dL, and ≥6.0 mg/dL.

- The mean number of flares requiring treatment from the end of the first year of treatment to the end of the study.
- Percentage of subjects with tophi resolution by the end of Years 1, 2, 3 and 4 for subjects with a primary palpable tophus at the Day 1 Visit.

Safety assessments will include: clinical laboratory results, adverse events (including rash events), and vital signs.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3B multicenter, randomized, double-blind, active-controlled study designed to evaluate the CV safety of febuxostat compared with allopurinol in subjects with gout and significant CV comorbidities. Approximately 7500 subjects will be randomly assigned to study medication treatment.

The overall duration of the study is dependent on the number of predefined MACE. The length of study is expected to be approximately 9 years. The length of study participation for each subject will vary due to the event driven study design. This study is designed to have a maximum of 624 MACE.

Subjects will be screened at Day -7 for entry. Subjects with cardiovascular comorbidities, gout and (1) a sUA ≥ 7 mg/dL or (2) with a sUA ≥ 6 mg/dL AND at least one flare in the 12 months prior to screening and/or the presence of tophi) and who meet the other selection criteria will be enrolled.

On Study Day 1/Randomization Visit, eligible subjects will be randomized in a 1:1 ratio to receive either febuxostat once daily (QD) or allopurinol QD. Randomization will be stratified based on baseline renal function: subjects with normal renal function or mild renal impairment (estimated creatinine clearance [(eCLcr) ≥ 60 mL/min] versus subjects with moderate renal impairment [eCLcr ≥ 30 but < 60 mL/min]).

Subjects randomized to febuxostat will initially receive the 40 mg dose QD. Subjects will remain on 40 mg remainder of the study if their sUA is < 6.0 mg/dL at the Week 2 Visit (± 3 days). If their sUA is ≥ 6.0 mg/dL at the Week 2 Visit (± 3 days) they will receive febuxostat 80 mg QD at Week 4 visit (± 3 days), and will remain on this dose for the remainder of the study. No dose adjustment will be made in the febuxostat based on renal function.

Subjects randomized to allopurinol who have normal renal function or mild renal impairment (eCLcr ≥ 60 mL/min) will initially receive allopurinol 300 mg QD with the dose increased in 100 mg increments monthly until either a sUA < 6.0 mg/dL or an allopurinol dose of 600 mg QD is achieved. Subjects randomized to allopurinol who have moderate renal impairment (eCLcr ≥ 30 but < 60 mL/min) will initially receive allopurinol 200 mg QD with the dose increased in 100 mg increments monthly until either a sUA < 6.0 mg/dL or an allopurinol dose of 400 mg QD is achieved.

To maintain the double-blind nature of the study, febuxostat and allopurinol tablets will be over-encapsulated and matching placebo capsules will be manufactured which are identical in appearance. Subjects will orally self administer 2 capsules each morning in the appropriate combination for their assigned dose and treatment. For details regarding the appropriate dose combination, please see Section 8.1.3.

Serum urate levels will be unblinded to the investigator and Takeda through the Week 10 Visit of the study to facilitate dose increases based on sUA response. After the Week 10 Visit, sUA measurements will be blinded to Takeda and the investigator. The interactive voice-activated

response system/interactive web-activated response system (IVRS/IWRS) will manage the treatment assignment at randomization and throughout the study medication treatment period.

Subjects currently on ULT will discontinue treatment at the Day -7 Screening Visit, and will begin colchicine 0.6 mg QD for gout flare prophylaxis. Subjects not on ULT will begin colchicine 0.6 mg QD on the Day 1/Randomization Visit. All subjects will receive gout flare prophylaxis for the first six months of the study medication treatment period. Alternatively, if colchicine is not tolerated and the subject's eCLcr is ≥ 50 mL/min, they will be administered naproxen 250 mg twice daily (BID) with lansoprazole 15 mg QD. If a subject has been maintained on an appropriate dose (as determined by the investigator) of another proton pump inhibitor (PPI) other than lansoprazole, he/she may continue treatment with it during this study. In instances when subjects should not receive colchicine or naproxen, other nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone may be provided at the investigator's discretion in accordance with the stated guidelines listed under the Excluded Medications and Treatments section of the protocol. In the event that colchicine, naproxen or other NSAIDs, proton pump inhibitors or prednisone are not tolerated or are contraindicated, the Investigator may choose not to use prophylaxis but to manage the subject's gout flares as they occur. Alternatively, if colchicine 0.6 mg daily is not tolerated by the subject, 0.6 mg every other day may be used. Following the Day 1 Visit, subjects will return for study visits during the first 3 months of the study based on the subject's sUA response. Once a subject sUA < 6.0 mg/dL there will be no further visits until Month 3 (Figure 6.b).

All subjects will return at Week 2 for measurement of sUA and all subjects will return for a Week 4 and Month 3 visit. If the Week 2 sUA level is < 6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Month 3. If the Week 2 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Week 6.

For the subset of subjects who have a Week 6 visit, if the Week 6 sUA level is < 6.0 mg/dL, the subject will be dispensed study medication at Week 8, and the next visit will occur at Month 3. If the Week 6 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 8 and the next visit will occur at Week 10.

For the subset of subjects who have a Week 10 visit, the subject will be dispensed study medication at the Month 3 visit. After the Month 3 visit, no further dose adjustments will be made. All subjects will have a Month 3 and Month 6 visits.

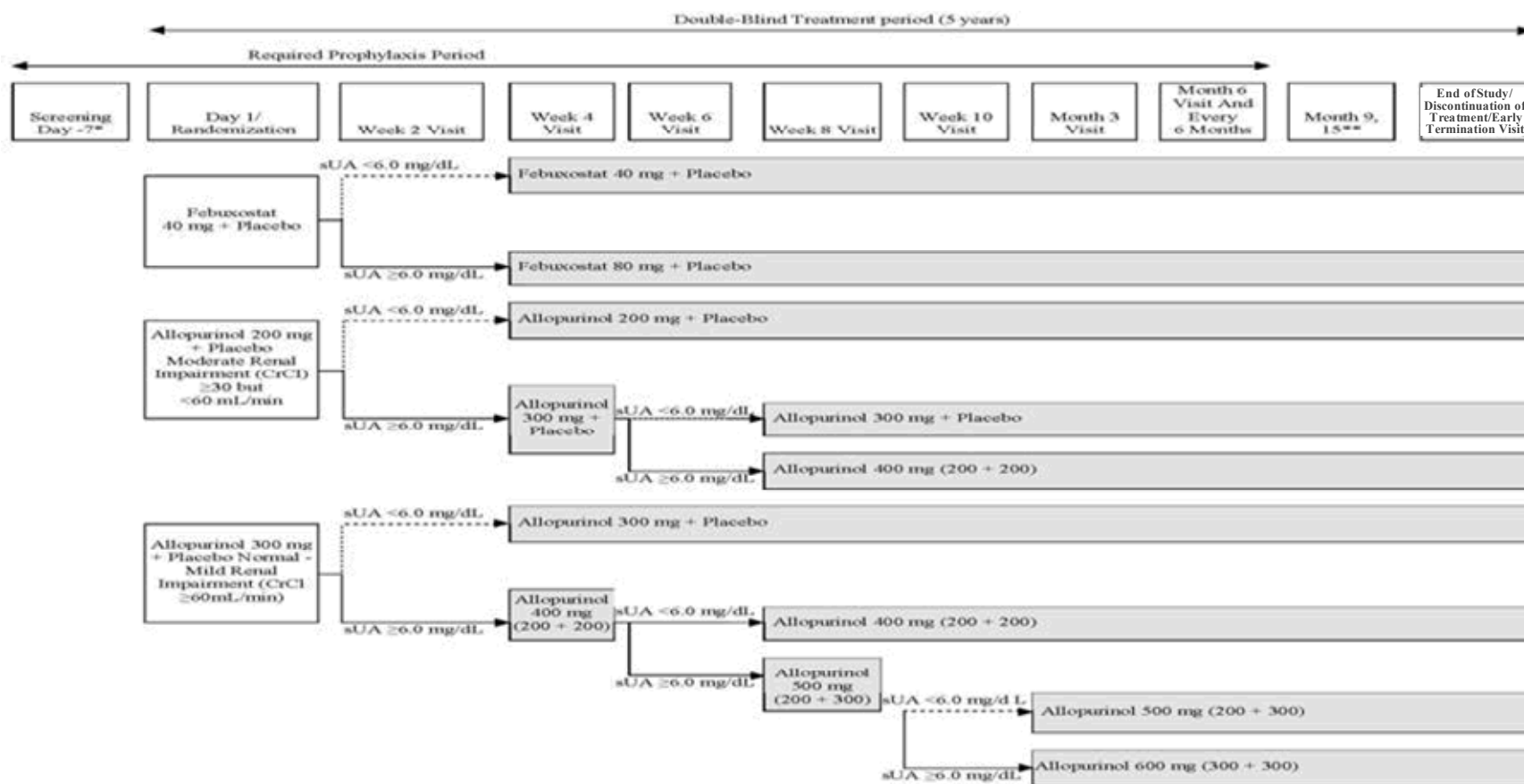
Following the Month 6 visit, all subjects will have visits every 6 months for the duration of the study. In addition, subjects with moderate renal impairment (eCLcr ≥ 30 but < 60 mL/min) and/or subjects who are elderly (≥ 65 years of age) will have visits at Month 9 and Month 15 to monitor the liver function tests (LFTs). Subjects who are withdrawn from study medication treatment but have not withdrawn consent will be contacted every 2 months for the duration of the study or until the subject experiences a CV event that is positively adjudicated as a MACE.

A Data Monitoring Committee (DMC) unblinded to the treatment assignment will periodically review results obtained in the enrolled into the study. An independent CV Endpoints Committee will be established to prospectively review all suspected CV events using blinded data. All

investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV SAEs. A CV worksheet will be provided to the investigational sites as a guide to ensure that supporting clinical information for each of these events are collected and compiled by the site and forwarded by fax or mail to Takeda Pharmacovigilance when available. The worksheet is not intended to be all inclusive and investigators should use medical judgment to determine what kind of supporting documentation should be collected

A schematic of the study design is presented in [Figure 6.a](#). A schedule of study procedures is listed in [Appendix A](#).

Figure 6.a Schematic of Study Design



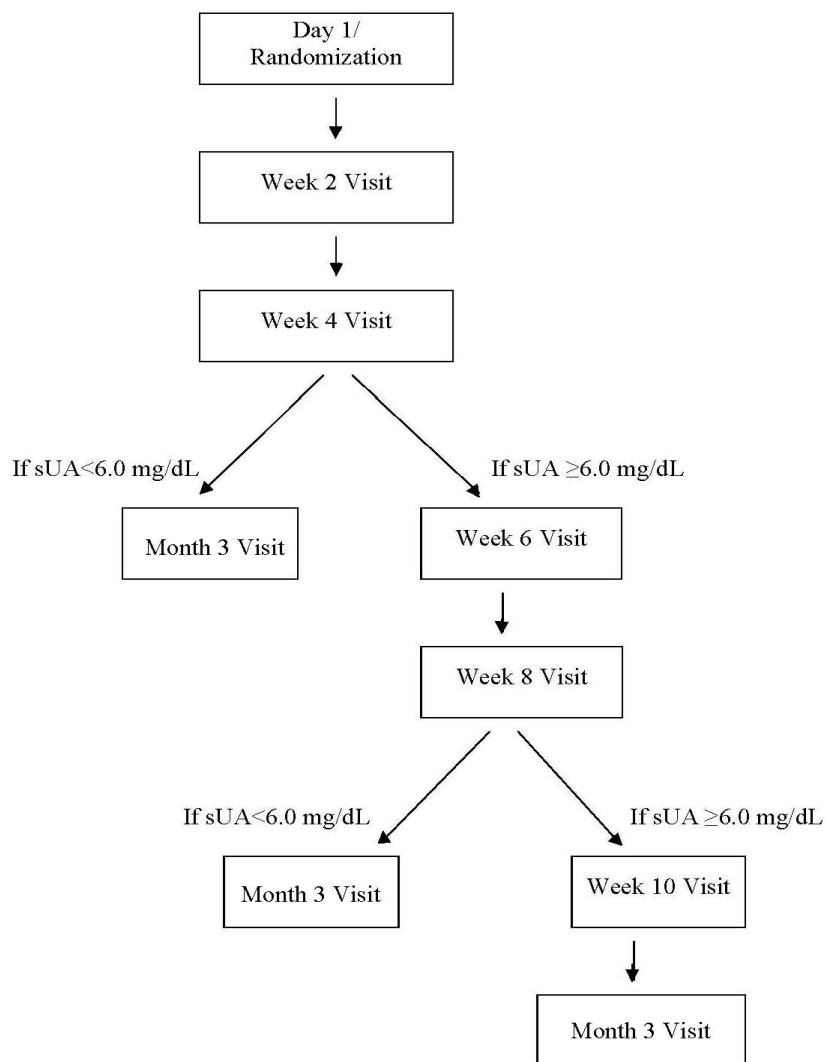
All subjects will receive 2 capsules daily in the morning.

*Screening period up to 7 days (Washout for subjects on ULT).

** Visit Month 9 and 15 for subjects with moderate renal impairment and/or elderly.

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Figure 6.b Schematic of Study Design for the First 3 months



6.2 Justification for Study Design, Dose, and Endpoints

In order to further explore the CV safety of febuxostat, Takeda has committed to conduct a randomized, controlled trial of adequate size and duration to determine whether the use of febuxostat is associated with a moderate increase in the risk of serious adverse CV outcomes as compared with allopurinol.

This study will enroll subjects with a high CV risk profile, characterized by the presence of documented cerebrovascular, coronary, or peripheral vascular disease, or the diagnosis of diabetes with microvascular or macrovascular complications. This randomized controlled study will attempt to enroll populations of interest including women (5%), elderly (20%), and renally impaired (30%).

The primary endpoint of the study will be a predefined composite of MACE events, including CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina with urgent coronary revascularization.

The overall duration of this study is dependent on the number of predefined MACE; however, the duration is expected to be approximately 9 years. The duration of treatment for each subject will vary (due to the event driven study design).

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless the following criteria are satisfied that require temporary suspension or early termination of the study.

1. New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Predefined study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit).
4. The Data Monitoring Committee recommends that the study should be suspended or terminated.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee, or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject or the subject's legally acceptable representative signs and dates a written, informed consent form prior to the initiation of any study procedures.
2. The subject is male ≥ 50 years of age or female ≥ 55 years of age and at least 2-years post-menopausal.
3. The subject has a history of major CV or cerebrovascular disease including at least 1 of the following:
 - MI.
 - Hospitalized unstable angina.
 - Cardiac or cerebrovascular revascularization procedure.
 - Stroke.
 - Hospitalized TIA.
 - Peripheral vascular disease (ankle brachial index ≤ 0.6 , revascularization and/or well-documented history of claudication).
 - History of diabetes mellitus with evidence of micro- or macrovascular disease (retinopathy, neuropathy, nephropathy, small vessel vascular diseases).
4. The subject has a history or presence of gout defined as having one or more of the American Rheumatism Association criteria for the diagnosis of gout [11]:
 - A tophus proven to contain urate crystals by chemical or polarized light microscopic means, AND/OR
 - Characteristic urate crystals in the joint fluid, AND/OR
 - History of at least 6 of the following clinical, laboratory, and x-ray phenomena:
 - More than 1 attack of acute arthritis.
 - Maximum inflammation developed within 1 day.
 - Monoarticular arthritis.
 - Redness observed over joints.
 - First metatarsophalangeal joint painful or swollen.
 - Unilateral first metatarsophalangeal joint attack.
 - Unilateral tarsal joint attack.
 - Tophus (proven or suspected).

- Hyperuricemia.
 - Asymmetric swelling within a joint on x-ray.
 - Subcortical cysts without erosions on x-ray.
 - Joint fluid culture negative for organisms during attack.
5. The subjects must have either:
- a sUA level ≥ 7.0 mg/dL (≥ 416 μ mol/L) at the Screening Visit **OR**
 - a sUA level ≥ 6.0 mg/dL (≥ 354 μ mol/L) at the Screening Visit **AND** inadequately controlled gout (≥ 1 flare in the 12 months prior to screening and/or the presence of tophi).
6. The subject is capable of understanding and complying with protocol requirements.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has secondary hyperuricemia (eg, due to myeloproliferative disorder, or organ transplant).
2. The subject has a history of xanthinuria.
3. The subject has received urate-lowering therapy (ie, febuxostat, allopurinol, probenecid, etc.) or excluded medication less than 7 days prior to Study Day 1/Randomization visit.
4. The subject has a known hypersensitivity to febuxostat or allopurinol or any components of their formulation.
5. The subject has active peptic ulcer disease.
6. The subject has a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the first dose of study medication.
7. The subject had MI or stroke within 60 days prior to the Screening Visit.
8. The subject has alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values greater than 2 times the upper limit of normal (\times ULN) during the Screening period.
9. The subject has a significant medical condition and/or conditions that would interfere with the treatment, safety, or compliance with the protocol.
10. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 5 years prior to the Screening Visit or the subject consumes >14 alcoholic beverages per week.
11. The subject has received any investigational medicinal product within the 30 days prior to the Screening Visit and throughout the study. In addition, the subject has been previously randomized in this study and received at least one dose of double blind study drug treatment.

12. The subject's estimated CL_{cr} is <30 mL/min, where CL_{cr} is calculated using the Cockcroft and Gault formula based on ideal body weight (IBW), as provided below:

$$\text{Estimated CL}_{\text{cr}} = \frac{(140 - \text{age [yr]}) \times (\text{IBW [kg]})}{72 \times (\text{serum creatinine [mg/dL]})} \text{ (women multiply by 0.85)}$$

Where IBW is 50 kg for men and 45.5 kg for women, plus 2.3 kg for each inch in height greater than 5 feet (60 inches).

13. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
14. The subject is required to take excluded medications listed in Section 7.3.2.
15. The subject has a known history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus.

7.3 Required Medications and Treatments

Subjects who meet the enrollment criteria will be randomized to 1 of 2 arms in a 1:1 ratio to receive either febuxostat or allopurinol at the Day 1/Randomization Visit via the IVRS/IWRS. Randomization will be stratified based on baseline renal function (subjects with normal renal function or mild renal impairment versus subjects with moderate renal impairment).

Subjects randomized to febuxostat will initially receive the 40 mg dose QD. Subjects will remain on 40 mg for the remainder of the study if their sUA is <6.0 mg/dL at the Week 2 visit. If their sUA is ≥6.0 mg/dL at the Week 2 visit, they will receive febuxostat 80 mg QD at the Week 4 visit and for the remainder of the study.

Subjects randomized to allopurinol with moderate renal impairment (estimated creatinine clearance [eCL_{cr}] ≥30 but <60 mL/min) will initially receive allopurinol 200 mg QD with the dose increased in 100 mg increments monthly until either a sUA <6.0 mg/dL or a maximum allopurinol dose of 400 mg QD is achieved. The titration of the allopurinol dose for these subjects will be completed at or by the Week 8 visit. If a subject achieves a sUA <6.0 mg/dL at a given dose of allopurinol, the subject will remain on that dose of allopurinol for the remainder of the study.

Subjects randomized to allopurinol, with normal renal function or mild renal impairment (eCL_{cr} ≥60 mL/min) will initially receive allopurinol 300 mg QD with the dose increased in 100 mg increments monthly until either a sUA <6.0 mg/dL or a maximum allopurinol dose of 600 mg QD is achieved. The titration of the allopurinol dose for these subjects will be completed at or by the Month 3 visit. If a subject achieves a sUA <6.0 mg/dL at a given dose of allopurinol, the subject will remain on that dose of allopurinol for the remainder of the study.

To maintain the double-blind nature of the study, febuxostat and allopurinol tablets will be over-encapsulated and matching placebo capsules will be manufactured which are identical in appearance. Subjects will orally self administer 2 capsules each morning (one capsule from each bottle) in the appropriate combination for their assigned dose and treatment. For details regarding the appropriate dose combination, please see Section 8.1.3. Serum urate levels will be unblinded to

Takeda and investigator through the Week 10 Visit of the study to facilitate dose increases based on sUA response. After the Week 10 Visit, sUA measurements will be blinded to Takeda and the investigator. The IVRS/IWRS will manage the treatment assignment after randomization and throughout the study medication treatment period.

For details regarding dosage form, manufacturing, packaging, and labeling please see Section 8.1.1.

The Sponsor will supply each site with bottles containing each of the gout flare prophylaxis medications: colchicine, naproxen, and lansoprazole. Prophylaxis medications can be taken on the morning of the study visit. The prophylaxis medications will remain unblinded. Drug accountability will be performed on all Takeda supplied prophylaxis medications.

7.3.1 Medications and Treatments Not Provided Directly by Sponsor

During the first six months subjects should be provided additional treatments as appropriate for gout flares by their study physician. In addition to dispensing the gout flare prophylaxis, the investigator may provide the subject with a prescription for an anti-inflammatory/analgesic agent of the investigator's choosing to be used in the event the subject experiences a gout flare during the study. The Investigator may use a reduced colchicine regimen (for example, colchicine 0.6 mg on alternate days) if required because of concomitant medications (medications with potential drug-drug interactions with colchicine, including verapamil, diltiazem, etc. (see Section 7.3.2), co-morbid conditions including chronic kidney disease, or patient preference based on prior experience with colchicine. Subjects should be provided additional treatments as appropriate for gout flares by their study physician. In addition to dispensing the gout flare prophylaxis, the investigator may provide the subject with a prescription for an anti-inflammatory/analgesic agent of the investigator's choosing to be used in the event the subject experiences a gout flare during the study.

After the first six months of gout flare prophylaxis, the United States (US) subjects only will be able to receive medication to treat gout flares during the study (eg, colchicine, naproxen and lansoprazole, Medrol dose pack, prednisone, indomethacin) using a prescription card to ensure they have adequate medications available to treat gout flares. The study physician should determine which medication is appropriate for each subject for treatment of gout flares.

These medications should be documented in the subject's source documents and on the appropriate electronic case report form (eCRF).

7.3.2 Excluded Medications and Treatments

Subjects may not take any medication (other than study medication) for the purpose of lowering sUA levels from at least 7 days prior to the Day 1 Randomization Visit to the End of Study/Discontinuation of Treatment/Early Termination Visit. Medications prescribed for another indication but which have an incidental urate lowering effect (for example losartan, fenofibrate) are not excluded.

Subjects who have taken any of the excluded medications listed below can be enrolled into the study if the excluded medication is discontinued at least 7 days prior to the Day 1 Randomization Visit. These medications may not be administered during the treatment phase. All medication use should be documented in the subject's source documents and on the appropriate eCRF.

Subjects who have terminated study drug but remain in the study (eg, bimonthly follow-up contacts) may have their gout treated in keeping with the physician's accepted practice.

Additionally, the following medications are not to be administered within 7 days prior to the Day 1 Randomization Visit and throughout the study medication treatment phase:

- Any urate-lowering drug other than study medication.
- Salicylates (chronic use of aspirin ≤ 325 mg/day is allowed).
- Azathioprine.
- Mercaptopurine.
- Theophylline.
- Intravenous colchicine.
- Pyrazinamide.
- Sulfamethoxazole/trimethoprim.
- Macrolides or ketolides, only when a subject is receiving concomitant colchicine.
- Subjects with renal or hepatic impairment should not be given colchicine in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

The following restrictions also apply during the study:

- Long-term (>4 continuous weeks) use of high dose corticosteroids (prednisone >10 mg/day or its equivalent) is not allowed. The chronic use of prednisone ≤ 10 mg/day (or its equivalent) and short-term use of higher doses of prednisone is allowed.
- Long-term use (>4 continuous weeks) of prescription or over-the-counter NSAIDs and cyclooxygenase 2 (COX-2) inhibitors, other than protocol required prophylaxis therapy supplied by Takeda, is not allowed.
- Short-term use of NSAIDs and COX-2 inhibitors is allowed (short-term use is defined as a duration of ≤ 4 weeks of continuous use).

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

7.4 Procedures for Discontinuation from Study Drug Treatment with Continued Participation in the Study via Follow-up Contacts

Subjects who discontinue study drug treatment will continue to participate in the study through follow-up contacts unless: consent is withdrawn by the subject; the subject experiences a CV event that is positively adjudicated as a MACE (the study team will notify the site in writing when it is no longer necessary to follow the subject with a positive MACE adjudication); the required number of study MACE events have occurred; or until the study is ended. Follow-up contacts will occur every 2 months (± 10 days).

The primary reason for permanent discontinuation of study drug treatment should be noted using the following categories:

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

NOTE: Subjects who experience ALT or AST $> 3 \times$ ULN in conjunction with elevated total bilirubin $> 2 \times$ ULN and satisfy the following 2 criteria: (1) The liver injury is hepatocellular in nature and there is not a prominent cholestatic component, or (2) there is no more likely alternative cause than drug induced liver injury, such as acute viral hepatitis A or B, or other acute liver disease, should be permanently discontinued from the study drug treatment.

2. Major protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from taking study drug treatment. The reason for withdrawal, if provided, should be recorded in the eCRF.

NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.

4. Pregnancy. The subject is found to be pregnant.
5. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
6. Study termination. The sponsor, IRB, ethics committee (EC), or regulatory agency terminates the study.
7. Other. The specific reasons should be recorded in the "specify" field of the eCRF.

The primary reason that the subject prematurely discontinued study drug should be listed on the End of Study Drug page of the eCRF. End of Study Drug eCRF should be completed when the subject discontinues study medication or completes the full cycle of study medication; end of Study Drug eCRF completion is independent of the decision to continue participation in the study via follow-up contacts.

These subjects should undergo all procedures required as part of the Discontinuation of Treatment Visit when the subject stops study drug treatment. In the event that these subjects later withdraw consent from participation in the study, an additional final Early Termination visit does not need to be performed.

At each follow-up contact, sites will ask the subject if they have taken any new medications (over the counter or prescription) since the last contact, or have stopped taking any ongoing medications recorded at the last contact. If yes, the generic medication name, start date, and end date and reason for use will be recorded on the Medication Information Obtained During Follow-up Contact eCRF.

Sites will also ask the subject at each follow-up contact if they have had any serious adverse events (SAEs) or any potential cardiovascular adverse events since the last contact. If yes, these will be recorded on the AE eCRF, and sites should follow the instructions in the Protocol Section 10.2.2, Collection and Reporting of SAEs if applicable. All SAEs should be followed up until resolution or permanent outcome of the event.

If the subject has had a potential serious CV event, he/she should bring the event related documents (labs, hospital discharge summary, etc) to the clinic. The study team will notify the site in writing upon a positive MACE adjudication when it is no longer necessary to follow a subject.

Efforts will be made to prevent any subject being lost to follow-up during the conduct of the study. Investigators should refer to Section 9.0 for gout flare assessment and Section 9.1.15 for gout flare treatment. Before a subject is considered lost to follow-up, a minimum of two documented telephone contact attempts must have been made and one certified letter must have been sent within 4 weeks of the most recently missed telephone call to the subject and/or emergency contact in an effort to contact the subject.

7.5 Procedures for Early Termination of a Subject from the Study (Both Drug and Visits)

A subject may discontinue his or her participation from the study without giving a reason at any time during the study. In addition, efforts should be made to perform all procedures required as part of the Early Termination Visit, even if the subject withdrew consent.

The primary reason for discontinuation of study participation should be noted using the following categories:

1. **Adverse Event.** A subject taking study medication has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the event. Also applies to subjects no longer taking study medication who are in follow-up who experience a serious CV event that is positively adjudicated as a MACE. NOTE: this reason is not intended to be selected for subjects in follow-up experiencing non-MACE AEs as these subjects can, and should, continue participation.
2. **Lost to follow-up.** The subject did not return to the clinic and/or attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented. Before a subject is

considered lost to follow-up, a minimum of two documented telephone contact attempts and one certified letter within 4 weeks of the most recently missed study visit must be sent in an effort to contact the subject.

3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
4. Major protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
5. Study termination. The sponsor, IRB, EC, or regulatory agency terminates the study.
6. Other. The specific reasons should be recorded in the "specify" field of the eCRF.

The primary reason that the subject prematurely discontinued planned study visits, including the planned follow-up contacts, should be listed on the End of Study Visits page of the eCRF. End of Study Visits eCRF should be completed when the subject discontinues from the study visits, including the follow-up contacts, independent of the decision to discontinue study medication.

Investigators should refer to Section 9.0 for gout flare assessment and Section 9.1.15 for gout flare treatment.

8.0 STUDY MEDICATION AND TREATMENTS

8.1 Study Medication and Treatments

Oral administration of:

- Over-encapsulated capsule containing 40 mg tablet of febuxostat (35 count [ct.] bottle).
- Over-encapsulated capsule containing 80 mg tablet of febuxostat (35 ct. bottle).
- Over-encapsulated capsule containing two 100 mg tablets of allopurinol (35 ct. bottle).
- Over-encapsulated capsule containing three 100 mg tablets of allopurinol (35 ct. bottle).
- One matching placebo capsule (35 ct. bottle).
- Over-encapsulated capsule containing 40 mg tablet of febuxostat (100 ct. bottle).
- Over-encapsulated capsule containing 80 mg tablet of febuxostat (100 ct. bottle).
- Over-encapsulated capsule containing two 100 mg tablets of allopurinol (100 ct. bottle).
- Over-encapsulated capsule containing three 100 mg tablets of allopurinol (100 ct. bottle).
- One matching placebo capsule (100 ct. bottle).
- Over-encapsulated capsule containing 40 mg tablet of febuxostat (200 ct. bottle).
- Over-encapsulated capsule containing 80 mg tablet of febuxostat (200 ct. bottle).
- Over-encapsulated capsule containing two 100 mg tablets of allopurinol (200 ct. bottle).
- Over-encapsulated capsule containing three 100 mg tablets of allopurinol (200 ct. bottle).
- One matching placebo capsule (200 ct. bottle).
- Prophylaxis treatment: colchicine 0.6 mg tablet (100 ct. bottle) OR naproxen 250 mg tablet (100 ct. bottle) and lansoprazole 15 mg capsule (30 ct. bottle) will be provided for the first 6 months.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Double-Blind Study Medication (febuxostat 40 mg, 80 mg and Allopurinol 200 mg, 300 mg)

Double-blind study medication will consist of over-encapsulated febuxostat 40 mg, febuxostat 80 mg, allopurinol 200 mg, allopurinol 300 mg and matching placebo capsules which are identical in appearance.

The capsules will be packaged into 3 different sizes of high density polyethylene bottles with child resistant caps containing 35 capsules, 100 capsules and 200 capsules each. Each bottle will bear a clinical label containing the pertinent study information, including the appropriate country-specific requirements and regulatory statements.

The over-encapsulation of febuxostat 40 mg, febuxostat 80 mg, allopurinol 200 mg, or allopurinol 300 mg tablets and the manufacturing of matching placebo capsules will be performed by PPD and A^{PPD} s. The packaging, labeling and distribution are also performed by PPD on behalf of Takeda Development Center Americas, Inc.

Gout Flare Prophylaxis Treatments

The commercial products provided for prophylaxis of gout flares (colchicine 0.6 mg or naproxen 250 mg and lansoprazole 15 mg) will be provided in the manufacturer's original packaging configurations. In addition, an ancillary label containing pertinent study information, including the appropriate country-specific requirements and regulatory statements, will be applied permanently to each bottle without covering the original manufacturer's product label. Package Inserts of the prophylaxis medication are available for further reference [12, 15,16].

Colchicine 0.6 mg tablets

Colchicine 0.6 mg tablets (PPD or Takeda Pharmaceuticals America, Deerfield, IL [formerly URL Pharma, Inc. / Mutual Pharmaceutical Company, Inc., Philadelphia, PA]) will be supplied in child resistant bottles containing 100 tablets each.

Naproxen 250 mg tablets

Naproxen (PPD will be supplied in child resistant bottles with 100 tablets, each tablet containing 250 mg of naproxen.

Lansoprazole 15 mg capsules

Subjects who are assigned to receive naproxen for gout flare prophylaxis will also be dispensed lansoprazole 15 mg capsules, to be taken in the morning prior to a meal, as protection against possible NSAID-associated peptic ulcers.

Lansoprazole (Takeda Pharmaceuticals America, Deerfield, IL) will be supplied in child-resistant bottles containing 30 capsules each.

8.1.2 Storage

All study medications supplied for the study must be kept in an appropriate, limited-access, secure location at the site and utilized according to sponsor's instructions and GCP until administered to study subjects or returned to TDC or its designee for destruction.

All double-blind study medication supplied for the study must be stored as follows:

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F-86°F).

Store of commercial medication should be in accordance with the manufacturer storage conditions.

The investigator should ensure that study medication is used only in accordance with the approved protocol. Study medication shall be dispensed only to subjects enrolled in the study.

8.1.3 Dose and Regimen

Double-Blind Study Medication (Febuxostat 40 mg, febuxostat 80 mg, allopurinol 200 mg, allopurinol 300 mg and matching placebo capsules)

Febuxostat (manufactured by PPD) and allopurinol (manufactured by PPD) tablets will be over-encapsulated to ensure blinding of study medication. The matching placebo capsule will ensure the blinding of the study medication. Subjects will orally self administer 2 capsules (one capsule from each bottle) each morning to receive one of the following:

- febuxostat 40 mg (1 capsule containing one 40 mg febuxostat tablet and 1 matching placebo capsule),
- febuxostat 80 mg (1 capsule containing one 80 mg febuxostat tablet and 1 matching placebo capsule),
- allopurinol 200 mg (1 capsule containing two 100 mg, allopurinol tablets and 1 matching placebo capsule),
- allopurinol 300 mg (1 capsule containing three 100 mg allopurinol tablets and 1 matching placebo capsule),
- allopurinol 400 mg (2 capsules each containing two 100 mg allopurinol tablets),
- allopurinol 500 mg (1 capsule containing two 100 mg allopurinol tablets and 1 capsule containing three 100 mg allopurinol tablets), OR
- allopurinol 600 mg (2 capsules each containing three 100 mg allopurinol tablets).

As specified in Section 6.0, febuxostat and allopurinol dose during the first 3 months of the study will be based on sUA level. Febuxostat, allopurinol, and matching placebo capsules will be identical in appearance.

Clinical supplies will be packaged, labeled, and distributed by PPD on behalf of Takeda.

The study sites will be supplied with the following study medication in a double-blind manner, blinded via over-encapsulation: febuxostat 40 mg tablet over-encapsulated (35 ct., 100 ct. and 200 ct. bottles), febuxostat 80 mg tablet over-encapsulated (35 ct., 100ct. and 200 ct. bottles), two allopurinol 100 mg tablets over-encapsulated (35 ct., 100 ct. and 200 ct. bottles) [200 mg dose], three allopurinol 100 mg tablets over-encapsulated (35 ct., 100 ct. and 200 ct. bottles) [300 mg dose] and matching placebo capsule (35 ct., 100 ct. and 200 ct. bottles). Capsules will be identical in appearance.

Each 35 ct, 100 ct. and 200 ct. bottle will bear a single-panel computer-generated label containing the required information, including the country-specific requirements and regulatory statements

contents, study medication number and spaces to enter subject's initials, subject number, and date dispensed.

During the treatment period, subjects should be advised to withhold the study medication on the scheduled visit days. If the subject does not withhold the study medication, the visit should not be rescheduled; however, the taking of the study medication must be recorded in the source document.

Gout Flare Prophylaxis Treatments

The prophylaxis medications will be provided in the manufacturer's original packaging configuration. In addition, an ancillary label containing pertinent study and subject information will be applied to each manufacturer's bottle without covering the product information.

Colchicine

Colchicine ^{PPD} [redacted] or Takeda Pharmaceuticals America, Inc. [formerly URL Pharma, Inc. / Mutual Pharmaceutical Company, Inc., Philadelphia, PA)] will be supplied in child-resistant bottles with 100 tablets each containing 0.6 mg of colchicine. Subjects should not receive colchicine if they have a history of hypersensitivity to colchicine. Subjects with renal or hepatic impairment should not be given colchicine in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses. In addition, the following warnings and precautions are noted for colchicine use:

- Fatal overdoses have been reported with colchicine in adults and children. Keep colchicine out of the reach of children.
- Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported with colchicine at therapeutic doses.
- Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment at therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, benzaifibrate or cyclosporine with colchicine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within one week to several months [12].
- Co-administration of colchicine with P-gp and/or CYP3A4 inhibitors have been demonstrated to alter the concentration of colchicine resulting in life-threatening interaction and death. The potential for drug-drug interactions must be considered prior to and during concomitant therapy with colchicine and diltiazem, verapamil, grapefruit juice, aprepitant, fluconazole, itraconazole, ketoconazole, cyclosporine, ranolazine, atazanavir, darunavir, indinavir, lopinavir, nefazodone, nelfinavir, ritonavir, squinavir, tipranavir, amprenavir and fosamprenavir. Colchicine dosage adjustment or alternate therapy should be considered [12],

- Monitor for toxicity and if present consider temporary interruption or discontinuation of colchicine [12].
- Avoid eating Seville oranges and drinking grapefruit juice

Subjects currently taking ULTs and who receive colchicine for gout flare prophylaxis will be dispensed 1 bottle of 100 tablets of colchicine 0.6 mg at the Day -7 Screening Visit. At Day 1/Randomization Visit, subjects will be redispensed the 1 bottle of 100 tablets dispensed at the Day -7 Visit. At the Month 3 visit, subjects will be dispensed 1 new bottle of 100 tablets of colchicine 0.6 mg. Subjects will orally self-administer a single dose of 0.6 mg colchicine QD beginning on the day that it is dispensed and continuing until the next study visit.

Subjects not currently taking ULTs and who receive colchicine for gout flare prophylaxis will be dispensed 1 bottle of 100 tablets of colchicine 0.6 mg at Day 1/Randomization Visit and at the Month 3 visit. Subjects will orally self-administer a single dose of 0.6 mg colchicine QD beginning on the day that it is dispensed and continuing until the next Study Visit.

The Investigator may use a reduced colchicine regimen (for example, colchicine 0.6 mg on alternate days) if required because of concomitant medications (medications with potential drug-drug interactions with colchicine, including verapamil and diltiazem but excluding those with potential strong interactions listed in Section 7.3.2), co-morbid conditions including chronic kidney disease, or patient preference based on prior experience with colchicine.

Subjects receiving colchicine for gout flare prophylaxis will return the previously dispensed bottle and any unused medication to the site at their next scheduled visit.

Drug Interaction: Macrolides, Ketolides, and Concomitant Colchicine

When a subject is receiving colchicine, the administration of a concomitant macrolide or ketolide is prohibited. An alternative antibiotic treatment option is recommended, when possible. However, if no alternative is available, a subject who is on colchicine for gout flare prophylaxis or treatment, and who requires treatment with a macrolide or ketolide must be temporarily discontinued from colchicine and switched to naproxen, when possible, for the duration of the macrolide or ketolide treatment and remain off of colchicine for 3 days following the last dose of the macrolide or ketolide. Subjects may resume colchicine on the fourth day following the last dose of the macrolide or ketolide. Subjects, who are temporarily switched from colchicine to naproxen for gout flare prophylaxis during the course of the macrolide or ketolide prescription, and for the 3 days following the last dose, should be provided with a prescription for naproxen for the duration they need to take it. However, if subjects are permanently switched from colchicine to naproxen as a result of requiring a concurrent macrolide or ketolide, the sites may contact the IVRS/IWRS to have naproxen supplies administered. If naproxen is not tolerated by a subject, the Takeda Medical Monitor should be contacted to discuss alternative prophylaxis options. Although it is preferred that a subject who requires a macrolide or ketolide be switched to naproxen (or an alternative prophylaxis), gout flare prophylaxis may be interrupted entirely, but is not recommended as the risk of a gout flare may increase. Subjects who are on naproxen for gout flare prophylaxis may take a concomitant macrolide or ketolide without stopping naproxen.

Naproxen

Naproxen ^{PPD} [16] will be supplied in child-resistant bottles with 100 tablets, each tablet containing 250 mg of naproxen. Subjects should not receive naproxen if they have a history of hypersensitivity to naproxen or any of its components, any other NSAID or aspirin or have active peptic ulcer disease. If colchicine is not tolerated by the subject and the subject has an eCLcr <50 mL/min, the investigator should contact the Takeda Medical Monitor for alternate prophylaxis treatment options.

Subjects currently taking ULTs and who receive naproxen with lansoprazole for gout flare prophylaxis, will be dispensed 2 bottles of naproxen 250 mg tablets at the Day - 7 Screening Visit. Subjects will orally self-administer a single dose of naproxen 250 mg BID, in the morning and in the evening with food, beginning on the day that it is dispensed and continuing until the next Study Visit.

Subjects not currently taking ULTs and who receive naproxen with lansoprazole for gout flare prophylaxis will be dispensed 2 bottles (100 counts) of naproxen 250 mg tablets at the Day 1/Randomization Visit and at the Month 3 Visit. Subjects will orally self-administer a single dose of naproxen 250 mg BID, in the morning and in the evening with food, beginning on the day that it is dispensed and continuing until the next Study Visit.

At Month 3, all subjects receiving naproxen for gout flare prophylaxis will return the previously dispensed bottle(s) and unused medication to the site and will receive another 2 bottles of naproxen 250 mg tablets.

Lansoprazole

Subjects who are assigned to receive naproxen for gout flare prophylaxis will also be dispensed lansoprazole 15 mg, to be taken in the morning prior to a meal, as protection against possible NSAID-associated peptic ulcers.

Lansoprazole [15] (Takeda Pharmaceuticals America, Deerfield, IL) will be supplied in 30 capsule bottles each capsule containing 15 mg of lansoprazole. Subjects should not receive lansoprazole if they have a history of hypersensitivity or intolerance to lansoprazole or any of its components.

Subjects currently taking ULTs and who receive lansoprazole will be dispensed 4 bottles of lansoprazole at the Day - 7 Screening Visit and Month 3 Visit. Subjects will orally self-administer a single dose of lansoprazole 15 mg in the morning, prior to a meal beginning on the day it is dispensed and continuing until the next study visit.

Subjects not currently taking ULTs and who receive lansoprazole will be dispensed 4 bottles of lansoprazole 15 mg at the Day 1/Randomization Visit and Month 3 Visit. Subjects will orally self-administer a single dose of lansoprazole 15 mg in the morning, prior to a meal beginning on the day it is dispensed and continuing until the next study visit.

All subjects receiving lansoprazole will return the previously dispensed lansoprazole bottles and unused study medication to the site.

Table 8.a Study Medication - Sponsor Supplied

Group	Study Medication	Dose
A	Febuxostat	1 capsule containing 40 mg or 80 mg febuxostat over-encapsulated AND 1 matching placebo capsule QD
B	Allopurinol	200 mg or 300 mg allopurinol over-encapsulated or matching placebo capsule QD in appropriate combination of two capsules for subject's dose of 200 mg, 300 mg, 400 mg, 500 mg or 600 mg
Prophylaxis medication will be provided for the first 6 months		
	Colchicine	0.6 mg tablet QD OR
	Naproxen	250 mg tablet BID AND
	Lansoprazole	15 mg capsule QD

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose of double-blind study medication (with or without associated adverse events) will be documented on an Overdose page of eCRF, in order to capture this important safety information consistently in the database. Adverse events associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

Febuxostat has been studied in healthy subjects in doses up to 300 mg daily for 7 days without evidence of dose-limiting toxicities. No overdose of febuxostat has been reported in clinical studies. Subjects should be managed by symptomatic and supportive care should there be an overdose.

There has been no clinical experience in the management of a subject who has taken massive amounts of allopurinol. Both allopurinol and oxypurinol are dialyzable; however, the usefulness of hemodialysis or peritoneal dialysis in the management of an overdose of allopurinol is unknown.

8.2 Randomization Code Creation and Storage

The Analytical Sciences department at Takeda or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel. Subjects will be randomized in a 1:1 ratio to receive either febuxostat or allopurinol. Randomization will be stratified based on baseline renal function (subjects with normal renal function or mild renal impairment versus subjects with moderate renal impairment).

8.3 Investigational Drug Blind Maintenance

The study medication blind will be maintained using the IVRS/IWRS, which will be accessed by the study sites for randomization and study medication assignments.

8.4 Investigational Drug Assignment and Dispensing Procedures

An IVRS/IWRS will be used for the study. Subjects will be assigned, in the order in which they are enrolled into the study, to receive their treatment according to the schedule allocated.

The investigator or the investigator's designee will contact the IVRS/IWRS to register the subject into the study at Screening. During this contact, the investigator or designee will provide the necessary subject-identifying information. At subsequent drug-dispensing visits, the investigator or designee will again contact the IVRS/IWRS to request additional investigational drug for a subject. The medication number of the investigational drug to be dispensed will be provided by the IVRS/IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the study medication is necessary for the medical treatment of the subject. The sponsor must be notified before the investigational drug blind is broken unless a medical emergency requiring unblinding occurs. In this case the investigator (or designee) at the site should contact the sponsor (see contact information listed in Section 1.1) within 24 hours.

For unblinding a subject, the investigational drug blind can be obtained by accessing the IVRS. Please refer to IVRS Unblinding Worksheet packet.

The date, time, and reason the blind was broken must be recorded in the source document and on the appropriate eCRF.

If the investigator is unblinded, investigational drug must be stopped immediately. Subjects will have the End of Study/Discontinuation of Treatment/Early Termination visit but will continue to be followed until the end of the study via follow-up contacts.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned.

Upon receipt of delivery of study medication and prophylaxis medications, the investigator (or investigator's designee) must access the IVRS/IWRS to confirm receipt of study medication and prophylaxis medications and verify the contents and condition of the shipment against the packing list. Any discrepancies between the packing list and the actual contents must be communicated to the assigned study monitor or a Takeda designee to resolve the issue. The packing list should then be filed in the investigator's essential document file. Once this process is completed, the study medication and prophylaxis medications should be stored in an appropriate, secure location as described in Section 8.0. Resupplies will be handled via IVRS/IWRS. The number of capsules/tablets dispensed and returned will be documented in the subject's source documents,

eCRF, and recorded on drug accountability logs retained with the investigator's essential document file.

The investigator must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all bottles used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must maintain a current inventory (Drug Accountability Log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and subject's use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication and amount dispensed, and the date and amount returned to the site by the subject, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain the copy of the original documentation regarding clinical study material accountability, return, and/or destruction, and the original will be sent to the sponsor.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the procedures to be completed at Screening and during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is found in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned via IVRS/IWRS to each subject at the time that informed consent is obtained and this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, alcohol use, and smoking status of the subject at Screening.

A complete medical, CV, and social history, will be obtained at Screening (at the time of informed consent). The general medical history will include a review of all major organ systems. The social history will include tobacco and alcohol use. The CV history will include CV medications and detailed history of prior CV procedures and/or events that stopped. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)).

Subjects will also be asked about their gout disease history, including frequency of acute gout attacks and the related symptoms experienced.

Medication history information to be obtained includes any medication stopped at or within 30 days prior to the Screening Visit, and will be documented in the subject's source documents and on the appropriate eCRF. Prior NSAID and aspirin use will be collected for the year prior to informed consent.

9.1.3 Physical Examination Procedure

A complete physical examination (defined as the pretreatment assessment immediately prior to the start of study medication) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) CV system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) genitourinary system (optional) and (12) other. All subsequent physical examinations should assess clinically significant changes from the baseline examination. A complete physical examination will be performed at Day 1, Month 12, and annually until End of Study/DoT/Early Termination.

9.1.4 Weight and Height Procedure

The subject's body weight will be collected (in kilograms) at Screening and End of Study/DoT/Early Termination. The subject's height will be collected at Screening. A subject should have weight and height measured while wearing indoor clothing and with shoes off.

9.1.5 Vital Sign Procedure

Vital signs will be obtained at **every scheduled clinic visit** ([Appendix A](#)). Vital sign measurements include: body temperature (oral), blood pressure (systolic and diastolic blood pressure), and pulse/beats per minute (bpm). Measurements will be made prior to dosing where applicable. One measurement of blood pressure and pulse will be measured while subjects are in a sitting position after they have been seated for at least 5 minutes and in accordance with American Heart Association guidelines (arm supported heart level, proper cuff size, etc).

9.1.6 Documentation of Concomitant Medications

At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from Screening through End of Study/DoT/Early Termination), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF, along with Reason for Use. Changes in medication for subjects that have discontinued treatment but remain in follow-up should be recorded on the Medication Information Obtained During Follow-up Contact eCRF, and not on the Concomitant Medications eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at Screening (at time of informed consent). This includes clinically significant laboratory, ECG, or physical examination abnormalities. The condition (ie, diagnosis) should be described, and the date that the condition began should be documented.

9.1.8 Procedures for Clinical Laboratory Samples

Laboratory samples will be taken at the time points stipulated in the Schedule of Study Procedures ([Appendix A](#)). All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cell count	ALT	Qualitative
White blood cell count with auto differential	Albumin	Appearance
Hemoglobin	Alkaline phosphatase	Color
Hematocrit	AST	pH
Platelet count	Total bilirubin	Specific gravity
Mean corpuscular volume	Total protein	Ketones
Mean corpuscular hemoglobin	Creatinine (b)	Protein
Mean corpuscular hemoglobin concentration	Blood urea nitrogen	Glucose
	Creatine kinase	Nitrite
	γ -Glutamyl transferase	Urobilinogen
	Potassium	Blood
	Sodium	
	Calcium	
	Magnesium	
	Glucose	
	Serum urate (a)	
	Triglycerides	
	Cholesterol	

OTHER:

Coagulation: prothrombin and activated partial thromboplastin time (only for subjects on warfarin)

International normalized ratio (only for subjects on warfarin)

Lipid panel (fasting) (c)

(a) sUA results will be unblinded to the Sponsor and study site through the Week 10 Visit.

(b) Estimated Creatinine clearance will be calculated by Central Lab.

(c) Lipid panel only at Day 1.

Serum urate values will be blinded to the Sponsor and study site after the Week 10 Visit. A member of the Takeda Pharmacovigilance Department, not involved with the febuxostat program, will be contacted by the central laboratory in the event of a serum urate value ≤ 2 mg/dL or > 18 mg/dL at any visit. The same non blinded member from Pharmacovigilance will follow up with the study site.

Subjects receiving warfarin will have the international normalized ratio (INR) in addition to prothrombin time and activated partial thromboplastin time monitored annually.

The central laboratory will perform laboratory tests. The results of laboratory tests will be returned (with the exception of sUA after Week 10 during the treatment period) to the investigator, who is responsible for reviewing and filing these results together with the source data in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.9 Pregnancy

Women of childbearing potential will not be included in this study; therefore, this study does not require any specific contraception.

If any subject is found to be pregnant during the study, she should be withdrawn from the study medication treatment phase. Any medication treatment and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, (eg, after Screening or within 30 days of the last dose of study medication) the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of her right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the subject agrees to the primary care physician being informed, the investigator should notify the subject's primary care physician that she was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor.

9.1.10 ECG Procedure

A standard 12-lead electrocardiogram (ECG) will be performed and recorded at the Day 1 and End of Study/ DoT/Early Termination, using the site's ECG equipment. The investigator will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Paper copies of the ECG tracings will be included in each subject's source document and details of the findings will be captured in the source and eCRF. For subjects who experience a CV AE that potentially meets the predefined MACE criteria, all available ECG tracings must be forwarded to the sponsor, along with all ECGs associated with the AE.

9.1.11 Documentation of Screen Failure

Investigators must account for all subjects who sign the informed consent form.

If the subject is found to be ineligible at the Screening Visit, and they have not taken a dose of prophylaxis medication, the site personnel should complete the screen failure eCRF. The IVRS/IWRS should be contacted as a notification of screen failure, and the primary reason for screen failure should be recorded in the eCRF.

The primary reason for screen failure is recorded using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specific inclusion/exclusion criteria should be recorded in the eCRF).
- Major protocol deviation.
- Lost to follow-up.

- Voluntary withdrawal of the consent (The reason for withdrawal, if provided, should be recorded in the eCRF).
- Study termination.
- Pregnancy.
- Other (The specific reason for withdrawal, if provided, should be recorded in the eCRF).

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.12 Documentation of Washout Failure

If the subject signs the informed consent, and takes at least one dose of prophylaxis medication, but does not randomize to double-blind study medication, they are considered a washout failure. The primary reason for washout failure is recorded using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (The specific inclusion criteria not met or the specific exclusion criteria met should be recorded in the eCRF.)
- Major protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal of the consent (The reason for withdrawal, if provided, should be recorded in the eCRF.)
- Study termination.
- Pregnancy.
- Other (The specific reason for withdrawal, if provided, should be recorded in the eCRF.)

9.1.13 Documentation of Study Entrance/Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be ineligible for randomization the investigator should record the primary reason for failure on the applicable eCRF.

9.1.14 Gout Flare Prophylaxis

All subjects will remain on gout flare prophylaxis for the first 6 months of the study.

Subjects currently on ULT will discontinue these treatments at the Day -7 Screening Visit, and will begin taking colchicine 0.6 mg QD for gout flare prophylaxis.

Subjects not currently taking ULT will begin taking colchicine 0.6 mg QD at the Day 1/Randomization Visit.

Alternatively, if colchicine is not tolerated by the subject and the subject's eCLcr is ≥ 50 mL/min they will be administered naproxen 250 mg BID with lansoprazole 15 mg QD.

In instances when subjects should not receive colchicine or naproxen, other NSAIDs or prednisone may be provided at the investigator's discretion in accordance with the stated guidelines listed under Excluded Medications and Treatments (Section 7.3.2). In the event that colchicine, naproxen or other NSAIDs, proton pump inhibitors or prednisone are not tolerated or are contraindicated, the Investigator may choose not to use prophylaxis but to manage the subject's gout flares as they occur. Alternatively, if colchicine 0.6 mg daily is not tolerated by the subject, 0.6 mg every other day may be used.

Prophylaxis medication is only provided until the Month 6 visit, but upon the Investigator's request, continued prescription may be allowed. Please note that study prescription cards intended to pay for acute gout flare medication cannot be used to pay for ongoing prophylaxis medication.

9.1.15 Treatment of Gout Flares

Subjects who experience a gout flare and who are taking colchicine for prophylaxis and have taken their daily dose, may take an additional colchicine 0.6 mg tablet at the onset of the flare, with another tablet one hour later, for a maximum of 3 tablets (1.8 mg) in a 24 hour period. After 12 hours, the original prophylaxis dose may be resumed [12].

Subjects experiencing a gout flare and who are taking naproxen for prophylaxis, may take naproxen 500 mg BID (2 additional doses of naproxen 250 mg) on the day the gout flare starts followed by 1 additional 250 mg dose on each subsequent day until the flare subsides. Gout flares may also be treated at the discretion of the investigator, as long as this treatment is in compliance with the prohibited medications for this study.

At the Day -7 Screening Visit in addition to dispensing the gout flare prophylaxis, the investigator should provide the subject with a prescription for an anti-inflammatory/analgesic agent of the investigator's choosing, to be used in the event the subject experiences a gout flare during the study and an increase of the prophylaxis medication dose is not efficacious in treating the flare. This may be done at the discretion of the investigator and in accordance with their practice guidelines.

Subjects are to be instructed to contact the investigator as soon as they begin to have a gout flare. An unscheduled visit can be conducted if deemed appropriate by the investigator. All subjects that experience flares while on the study will have the option to receive acute gout flare treatment if deemed appropriate by the principal investigator. The investigator may also consult with the Takeda Medical Monitor for further discussion. A Gout Flare Assessment Worksheet (sample shown in [Appendix G](#)) will be used to collect the gout flare information.

9.1.16 Gout Flare Assessment

Subjects will be assessed for gout flares beginning at the Day -7 Screening Visit and throughout the duration of the study. Subjects are to be instructed to call the investigator as soon as they think they may be having a gout flare. The Gout Flare Assessment Worksheet, developed with

Drs. Schumacher, Gaffo, Saag and Singh [13] (sample shown in [Appendix G](#)) will be completed by the site personnel (ie, study coordinator, study nurse, or the investigator).

All gout flares should be followed until complete resolution. Subjects should be instructed to contact the site when the flare has resolved (typically 7-10 days after onset). The study site will contact the subject 7 days after the initial report if the subject fails to report the end date of the gout flare. The attempts to contact the subject to obtain the end date of the gout flare must be documented (2 documented telephone contact attempts).

Subjects will be instructed to report the following information: the onset and end date of the flare, the kind of prophylaxis medication they are taking at the time of the event, whether or not the attack required medication (including type) and dates of treatment, the location of the flare, signs and symptoms regarding the flare including: swelling, redness, tenderness and joint warmth the worst pain of the gout flare (pain at rest), the assessment of current gout flare compared with all previous gout flares in any joints. The investigator will review the information provided and assess whether or not they believe the subject experienced a gout flare and/or document an alternative etiology.

The Gout Flare Assessment Worksheet will be maintained with the subject's source documents. All confirmed gout flares will be transcribed from the worksheet onto the Gout Flare eCRF page. These entries should not to be documented on the Adverse Event eCRF (unless they meet SAE criteria). If the investigator feels it is appropriate, an unscheduled visit may be scheduled.

9.1.17 Physical Assessment of Tophi

Subjects will be assessed for the presence of tophi by palpation at the Day 1 visit. The most easily identified and palpable tophus will be designated as "primary" and the presence or absence of this tophus should be assessed annually and at the End of Study/DoT/Early Termination visit. In addition, all tophi will be counted and the number recorded on the Tophi eCRF page at all tophi assessment visits.

9.1.18 Rash Assessment

AEs of rash will be collected beginning at the Day -7 Visit until 30 days after study medication is discontinued. AEs of rash will be documented on the Rash Adverse Event Worksheet (sample shown in [Appendix F](#)) that will be maintained with the subject's source documents. Rash AEs recorded on the Rash Adverse Event Worksheet will be transcribed over to the Adverse Event eCRF. So long as the event is not deemed a SAE, the completed Rash Adverse Event Worksheet will be faxed to Takeda, in accordance with the instructions on the worksheet, within 48 hours of the site's knowledge of the event. If the event is deemed a serious adverse event, follow procedure in [10.2.2](#).

9.1.19 Management, Withdrawal and Follow-Up of Subjects With Liver Enzyme Elevations

If the ALT or AST value rises to $>3 \times \text{ULN}$, laboratory tests (at minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, and INR) should be repeated within 48 to 72 hours. If the ALT or AST value remains elevated $>3 \times \text{ULN}$ when repeated, and this observation cannot be

explained by concomitant disease or another alternative etiology, the abnormality must be recorded as an AE, if it has not already. In these cases, additional tests are required to rule out other etiologies. The investigator must contact the Takeda Medical Monitor for determination of additional testing, consideration of immediate discontinuation of study medication, discussion of the relevant subject details, and possible alternative etiologies.

In addition, study medication should be temporarily discontinued with appropriate clinical follow-up, including repeat laboratory tests, until a subject's laboratory profile has returned to normal, if the following circumstances occur at any time during study medication treatment phase:

- ALT or AST $>8 \times \text{ULN}$, or
- ALT or AST $>5 \times \text{ULN}$ and persists for more than 2 weeks, or
- ALT or AST $>3 \times \text{ULN}$ in conjunction with elevated total bilirubin $>2 \times \text{ULN}$ **or** INR >1.5 , or
- ALT or AST $>3 \times \text{ULN}$ with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($>5\%$).

Subjects who experience ALT or AST $>3 \times \text{ULN}$ in conjunction with elevated total bilirubin $>2 \times \text{ULN}$ and who also satisfy one of the following criteria should be permanently discontinued from the study medication treatment phase:

- The liver injury is hepatocellular in nature and there is not a prominent cholestatic component; or
- There is no more likely alternative cause than drug induced liver injury, such as acute viral hepatitis A or B, or other acute liver disease.

Additional information will be collected in the eCRF for liver enzyme AEs that cannot be explained by concomitant disease. This information will include recent history (if any), of alcohol use, blood transfusions, occupational/toxic exposure, tattooing, recreational drug use, special diet, surgery/general anesthesia, travel, or use of herbal supplements or teas. This information will also include signs and symptoms (if any) associated with the AE and results of any additional diagnostic tests performed.

9.2 Monitoring Subject Compliance

Subjects will be required to bring study medication containers to each clinic visit, regardless of whether the study medication container is empty.

If a subject is persistently noncompliant with the sponsor-supplied double blind study drugs ($<80\%$ or $>120\%$ of the allocated medication for the period since the last visit) it may be appropriate to withdraw the subject from the study medication treatment and continue in the study to monitor for potential CV events. All subjects should be reinstructed about the dosing requirement during study visits. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s). Study days/weeks and visit windows should be calculated after randomization and should be calculated from the day of the first dose of double-blind treatment (Day 1).

The overall duration of the study is dependent on the number of the predefined MACE; the study will end when the required number of events has accrued. The duration of the study is expected to be 9 years. The length of study participation for each subject will vary (due to the event driven study design).

Subjects are required to bring all of the Sponsor supplied medication to every visit.

9.3.1 Screening

Subjects will be evaluated for enrollment based on all inclusion/exclusion criteria. Subjects will be evaluated for enrollment based on their prior history of a major CV or cerebrovascular event. Subjects currently receiving ULT will begin the 7 day washout and should receive prophylaxis medication.

If a subject has a gout flare at the Screening Visit, the visit procedures should be delayed and the subject should be treated for the gout flare and return to the study site no earlier than 2, but no later than 3, weeks after the resolution of the flare. Please contact the Medical Monitor if randomization does not occur within four weeks of the Screening visit. Screening may be less than 7 days for subjects not washing off of ULTs. Screening period may be up to 28 days depending on whether subject has a flare or requires a repeat sUA test.

Procedures to be done at Screening Day -7 to Day -1

- Obtain informed consent.
- Review of inclusion/exclusion criteria.
- Demographics, medical, gout, social, CV and medication history.
- Access IVRS/IWRS to obtain the subject number and dispense prophylaxis medication (for subjects discontinuing prior ULT at Day -7).
- Concurrent medical conditions.
- Vital signs.
- Weight and height.
- Assess for pre-treatment events.
- AEs assessment (for subjects discontinuing prior ULT at Day -7).
- Gout flare assessment.
- Laboratory assessments.

- Concomitant medications assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Dispense prescription for additional gout flare medication.

All subjects who do not meet the sUA inclusion criteria but meet all remaining criteria will be allowed to have one repeat sUA test. This additional test should occur no earlier than two weeks but no later than three weeks after the initial test.

9.3.2 Study Randomization

Study Randomization will take place on Day 1. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS, as described in Section 8.4. Subjects will be asked to take the first dose of study medication in the office after randomization, as described in Section 8.4. The procedure for documenting Screening failures is provided in Section 9.1.11.

If a subject has a gout flare at the Randomization (Day 1) Visit, the visit procedures should be delayed and the subject should be treated for the gout flare and return to the study site no earlier than 2 but no later than 3 weeks after the resolution of the flare. If the subject had a flare that started after the screening visit, the randomization visit procedures should be delayed until no earlier than 2 but no later than 3 weeks after the resolution of the flare.

The following procedures will be performed and documented during Study Randomization:

- Review of inclusion/exclusion criteria.
- Access IVRS/IWRS and dispense assigned study medication with dosing instructions.
- Physical examination.
- Collect vital signs.
- Tophus assessment (includes primary tophus assessment and counting of all other tophi).
- Collect laboratory assessments (fasting if at all possible, however if the subject is not fasting continue with visit).
- 12-lead ECG.
- Assess for pretreatment events.
- AEs assessment.
- Gout flare assessment.
- Concomitant medication assessment.
- Dispense prophylaxis medication, with dosing instructions (for subjects not taking ULTs at Screening).
- Educate subject on reporting of potential CV events and gout flares.

- Assess compliance of prophylaxis medication and re-dispense (for subjects discontinuing prior ULT at Day -7).
- Verify subject's contact information (including details of emergency contact).
- Review the Retention Program (subjects in the US and Canada only). Unless subjects opt-out, enroll them in the program.
- Review the Gout Flare brochure.

9.3.3 Treatment Phase

All scheduled visits should occur in the morning, if possible. During the treatment period, subjects should be advised to withhold double blind study medication on scheduled visit days. If the subject does not withhold the study medication, the visit should not be rescheduled; however, the taking of the study medication must be recorded in the source document. If a subject has a gout flare during the treatment phase, the visit does not need to be re-scheduled.

9.3.3.1 Week 2 (± 3 Days)

All subjects will return at Week 2 for measurement of sUA.

The following procedures will be performed at Week 2:

- Vital signs.
- AE assessment.
- Gout flare assessment
- Laboratory assessments.
- Concomitant medication assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Assess compliance of the study medication and re-dispense.
- Assess compliance of prophylaxis medication and re-dispense.
- Verify subject's contact information (including details of emergency contact).

9.3.3.2 Week 4 (± 3 Days)

If the Week 2 sUA level is <6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Month 3.

If the Week 2 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 4, and the next visit will occur at Week 6.

The following procedures will be performed at Week 4:

- Access IVRS/IWRS and dispense assigned study medication with dosing instructions.

- Vital signs.
- AE assessment.
- Gout flare assessment.
- Concomitant medication assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Collect unused study medication and assess compliance.
- Assess compliance of prophylaxis medication and re-dispense.
- Verify subject's contact information (including details of emergency contact).

9.3.3.3 Week 6 (± 3 Days)

For the subset of subjects who have a Week 6 visit the following procedures will be performed:

- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- Concomitant medication assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Assess compliance of study medication and re-dispense.
- Assess compliance of prophylaxis medication and re-dispense.
- Verify subject's contact information (including details of emergency contact).

9.3.3.4 Week 8 (± 3 Days)

For the subset of subjects who have a Week 8 visit:

If the Week 6 sUA level is <6.0 mg/dL, the subject will be dispensed study medication at Week 8, and the next visit will occur at Month 3.

If the Week 6 sUA level is ≥ 6.0 mg/dL, the subject will be dispensed study medication at Week 8 and the next visit will occur at Week 10.

The following procedures will be performed at Week 8:

- Access IVRS/IWRS and dispense assigned study medication with dosing instructions.
- Vital signs.
- AE assessment.

- Gout flare assessment.
- Concomitant medication assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Collect unused study medication and assess compliance.
- Assess compliance of prophylaxis medication and re-dispense.
- Verify subject's contact information (including details of emergency contact).

9.3.3.5 Week 10 (± 3 Days)

For the subset of subjects who have a Week 10 visit, the subject will be dispensed study medication at the Month 3 visit. After the Month 3 visit, no further dose adjustments will be made.

The following procedures will be performed at week 10:

- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- Concomitant medication assessment.
- Educate subject on reporting of potential CV events and gout flares.
- Assess compliance of study medication and re-dispense.
- Assess compliance of prophylaxis medication and re-dispense.
- Verify subject's contact information (including details of emergency contact).

9.3.3.6 Month 3 (± 3 Days)

The following procedures will be performed at Month 3:

- Access IVRS/IWRS and dispense assigned study medication with dosing instructions.
- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- Concomitant medication assessment.
- Dispense new prophylaxis medication.
- Collect unused prophylaxis medication and assess compliance.

- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares.
- Verify subject's contact information (including details of emergency contact).

9.3.3.7 Month 6 (± 3 Days)

- Access IVRS/IWRS and dispense assigned study medication with dosing instruction.
- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- Concomitant medication assessment.
- Collect unused prophylaxis medication and assess compliance.
- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares and possibility of obtaining the prescription card to obtain medication to treat gout flares (only in the US).
- Verify subject's contact information (including details of emergency contact).
- Review the Retention Program (subjects in the US and Canada only).
- Review the Gout Flare Brochure.

9.3.3.8 Months 9, 15 (Elderly and/or Moderately Renally Impaired Subjects) (± 7 Days)

- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- Concomitant medication assessment.
- Educate subjects on reporting of potential CV events and gout flares.
- Assess compliance of double blind medication.
- Verify subject's contact information (including details of emergency contact).

9.3.3.9 Month 12 and Every 6 Months Until End of Study/Discontinuation of Treatment/Early Termination (± 7 Days)

- Access IVRS/IWRS and dispense assigned study medication with dosing instruction.

- Physical examination (performed annually).
- Vital signs.
- Tophus Assessment (performed annually for subjects with tophi present).
- AE assessment.
- Gout flare assessment.
- Laboratory assessments (fasting if at all possible, however if the subject is not fasting continue with visit).
- Concomitant medication assessment.
- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares and possibility of obtaining the prescription card to obtain medication to treat gout flares (only in the US).
- Verify subject's contact information (including details of emergency contact).

9.3.3.10 End of Study/Discontinuation of Treatment/Early Termination

All efforts should be made to prevent any subject being lost to follow-up during the conduct of the study.

Subjects who either discontinue study drug treatment, or who fully withdraw consent, should complete the following procedures at their Discontinuation of Treatment Visit or Early Termination Visit, respectively. For subjects who are active in the study (taking study medication) at the time the independent CV Endpoints Committee determines that the targeted number of adjudicated MACE have been reached, instructions will be provided by the Sponsor regarding the scheduling of the End of Study Visit, which includes the following procedures.

- Access IVRS/IWRS to complete the subject or for Early Termination.
- Physical examination.
- Vital signs.
- Weight.
- Tophus assessment.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments (fasting if at all possible, however if the subject is not fasting continue with visit).
- 12-lead ECG.
- Concomitant medication assessment.

- Collect unused study medication and assess compliance.
- Collect unused prophylaxis medication (if applicable).

For all subjects receiving any Sponsor supplied medication, the investigator must complete both the End of Study Drug eCRF page and the End of Study Visit eCRF page.

9.3.3.11 Unscheduled Visit (if applicable)

Subjects may return to the study center for unscheduled visits, as needed. If a subject presents to the study site for an Unscheduled Visit, the date and reason for the Unscheduled Visit must be documented on the Unscheduled Visit eCRF page. In addition, if study medication is dispensed or if procedures are completed (for example: physical examination, vital signs), the information must be documented on the appropriate eCRF and in the subject's source documents. Sites must call the IVRS/IWRS if additional drug is dispensed.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for Pretreatment Events and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should be not considered PTEs or AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a pretreatment event(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be pretreatment events or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not

considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a pretreatment event or as an AE.
- If the ALT or AST value rises to $>3 \times \text{ULN}$, laboratory tests (at minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, and INR) should be repeated within 48 to 72 hours. If the ALT or AST value remains elevated $>3 \times \text{ULN}$ when repeated, and this observation cannot be explained by concomitant disease or another alternative etiology, the abnormality must be recorded as an AE, if it has not already.
- Pre-existing conditions: Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as pretreatment events or AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a pretreatment event (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of...").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg, "worsening of...").
- If a subject has a degenerative concurrent condition (eg, cataracts), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").

Worsening of pretreatment or AEs:

- If the subject experiences a worsening or complication of a pretreatment event after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").

Changes in severity of AEs/PTEs/SAEs:

- If the subject experiences changes in severity of an AE/PTE/SAE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered pretreatment events or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a pretreatment event or an AE. Complications resulting from any planned surgery should be reported as adverse events.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as pretreatment events or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as adverse events.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered pretreatment events or AEs, but will instead be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires subject HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.

- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term
1. Acute respiratory failure/acute respiratory distress syndrome.
2. Torsade de pointes/ventricular fibrillation/ventricular tachycardia.
3. Malignant hypertension.
4. Convulsive seizures.
5. Agranulocytosis.
6. Aplastic anaemia.
7. Toxic epidermal necrolysis/Stevens-Johnson syndrome.
8. Hepatic necrosis.
9. Acute liver failure.
10. Anaphylactic shock.
11. Acute renal failure.
12. Pulmonary hypertension.
13. Pulmonary fibrosis.
14. Neuroleptic malignant syndrome/malignant hyperthermia.
15. Spontaneous abortion/stillbirth and fetal death.
16. Confirmed or suspected transmission of infectious agent by a medicinal products.
17. Confirmed or suspected endotoxic shock.
Note:
1. As a general rule, the event terms mentioned in the list above should be handled as “serious.”
2. This list is applicable when any of the above terms are reported as the newly occurred event after drug administration.

Pretreatment events that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.2.3).

10.1.5 Severity of Pretreatment Events and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Yes:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
No:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all pretreatment events and AEs.

The relationship should be assessed as "Yes" if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as "No".

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 Pretreatment Event and AE Collection Period

Collection of pretreatment events will commence from the time the subject signs the informed consent to participate in the study and continue until either the administration of sponsor-supplied gout flare prophylaxis on Day -7 for subjects requiring ULT washout, or administration of double-blind medication at Day 1 for subjects not requiring ULT washout. For subjects who discontinue prior to any prophylaxis or double-blind study drug administration, pretreatment events are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that subjects are administered sponsor-supplied medication, which is at Day -7 for subjects requiring ULT washout, or administration of double-blind medication at Day 1 for subjects not requiring ULT washout. Subjects will be instructed at their last study visit to call and report any AEs that occur within 30 days of last dose of study medication and any potential CV events until the completion of the study. All adverse events

will be reported in detail on the appropriate eCRF and followed to a satisfactory conclusion (ie. until the adverse event resolves, and returns to baseline, or becomes stabilized).

10.2.1.2 Pretreatment Event and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study.

All non-SAEs that occur will be collected from the time the informed consent form is signed.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All pretreatment events and AEs will be documented in the pretreatment event/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Severity.
- Investigator’s opinion of the causal relationship between the event and administration of study drug(s) (the relationship should be assessed as “Yes” if the investigator considers that there is reasonable possibility that an event is due to study drug (double-blind or prophylaxis). Otherwise, the relationship should be assessed as “No”) (not completed for pretreatment events).
- Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study drug (not applicable for pretreatment events).
- Outcome of event.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs after informed consent through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed in English and signed by the investigator immediately or within 1 working day of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 1 working day to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 1 working day of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.4 Safety Reporting to Investigators, IRBs or ECs, and Regulatory Authorities

The sponsor will be responsible for reporting all applicable SAEs to regulatory authorities, investigators and IRBs or ECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

For all active investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the study medication, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs or ECs according to all applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to his or her IRB or EC.

10.2.5 Evaluation of CV Safety

Each death and selected serious cardiovascular adverse events, including any medically significant updates, will be sent by Takeda to a blinded CV Endpoints committee (see Section 11.2) for adjudication. The final selection of the CV events for adjudication is done by the adjudication committee chair. Non-serious, potential CV events will not be adjudicated.

All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and selected CV SAEs. A CV worksheet will be provided to the investigational sites as a guide to ensure that supporting clinical information for each of these events are collected and compiled by the site and forwarded to Takeda Pharmacovigilance when available. The worksheet is not intended to be all inclusive and investigators should use medical judgment to determine what additional supporting documentation should be collected.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent DMC

An independent DMC will be established to monitor the progress and the overall safety of subjects enrolled in this study. This committee will periodically review study safety data and make recommendations to Takeda as appropriate to ensure the safety of subjects. The committee will comprise of external consultants who have expertise in the conduct and review of clinical trials. Details of the DMC membership and responsibilities will be described in the DMC charter. The recommendations by the DMC based upon their review of the data will be communicated to the Sponsor.

11.2 CV Endpoints Committee

An independent CV Endpoints Committee consisting of 3 cardiovascular experts will be established to prospectively review and adjudicate all suspected cardiovascular events in a blinded fashion to determine if the reported event meets the criteria for MACE.

The procedures and rules of adjudication of these events by the CV Endpoints Committee will be described in a separate charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, pretreatment events, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject.

The sponsor or its designee will supply investigative sites with eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Corrections to eCRFs include an audit trail that captures the old information, the new information, the name of the person making the correction, the date the correction was made and the reason for change. The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRF page as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs are accessed through the Medidata remote data capture application, which allows for on-site data entry and data management. Site users can read from and write to the Sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study at each site will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors for completeness and acceptability. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed original eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Each study site will have access to the study data in Medidata until they receive a CD of all subject data in PDF format after database lock. Furthermore, International Conference on Harmonisation (ICH) 4.9.5 requires

the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the first subject enrolled. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A periodic blind data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The primary endpoint and all other analyses by treatment group will be analyzed according to the randomized treatment using the Full Analysis Set (FAS). The FAS will consist of all subjects who were randomized and received at least one dose of double-blind study medication. If a subject reports a composite MACE after treatment discontinuation, then the reported event will be counted toward the treatment to which they were randomized.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (eg, age, race, gender, height, weight, body mass index [BMI], sUA) will be summarized using descriptive statistics for each treatment group and overall (eg, mean, SD, median, minimum, and maximum values, and the number and percent of subjects in specified categories). For categorical variables (eg, race, gender) the number and percent of subjects in specified categories will be presented. Unless otherwise specified, descriptive statistics on continuous variables (eg, age, height, weight, BMI, sUA) will consist of the number of subjects (N), mean, SD, minimum, 25th percentile, median, 75th percentile, and maximum. Gout history and CV history will also be summarized.

13.1.3 Safety Analyses

Safety will be assessed by evaluating the incidence of adverse events including pre-defined MACE, laboratory tests and vital signs. A blinded CV Endpoints Committee will adjudicate each death and selected serious cardiovascular adverse event to determine if the event meets the MACE criteria.

13.1.3.1 CV Safety Analysis

Assuming constant proportional hazards, the hazard ratio for the primary endpoint will be computed based on febuxostat and allopurinol estimated hazard rates. The febuxostat treatment group will be compared to the allopurinol treatment group to test for non-inferiority in the MACE composite rate using a Cox proportional hazards model with treatment and baseline renal function as factors in the model. Non-inferiority of febuxostat to allopurinol will be declared at an interim or at the final analysis if the current upper 1-sided CI for the hazard ratio calculated with critical

values obtained using the Lan-DeMets-O'Brien-Fleming alpha spending function, which preserves an overall 1-sided false-rejection rate of 2.5%, is less than 1.3.

Analysis of the secondary and other cardiovascular endpoints will be conducted similarly using a Cox proportional hazards model. No adjustments will be made for multiplicity.

Additional analysis on the primary safety endpoint will be performed using Cox-proportional hazards model controlling for the effect of NSAIDs use. The model will include treatment group, baseline renal function, and use of NSAIDs as explanatory variables. A similar analysis will control for the effect of low-dose aspirin use.

13.1.3.2 Other Safety Analysis

Treatment-emergent AEs will be summarized using the MedDRA coding dictionary. In general AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE), the MedDRA system organ class (SOC), the MedDRA high level term (HLT), and the MedDRA preferred term (PT). Tabulations at each level of a term will present count (n) and percentage of subjects reporting any event for that term. Subjects reporting more than one occurrence for the term (level) being summarized will be counted only once.

13.1.4 Efficacy Analysis

The percentage of subjects whose average sUA level during the period from the end of the first year of treatment to the end of the study will be summarized, using the following categories <4.0 mg/dL, ≥ 4 to <5.0 mg/dL, ≥ 5 to <6.0 mg/dL, and ≥ 6.0 mg/dL.

The flare rate from the end of the first year of treatment to the end of the study will be summarized by the average sUA level during the period from the end of the first year of treatment to the end of the study, using the following categories <4.0 mg/dL, ≥ 4 to <5.0 mg/dL, ≥ 5 to <6.0 mg/dL, and ≥ 6.0 mg/dL. Flare rate will be calculated as the number of flares from the end of the first year of treatment to the end of the study divided by the length of time on treatment during the period after the first year and through the end of the study.

The percentage of subjects with tophi resolution by the end of Year 1, 2, 3, and 4 will be summarized by the average sUA level during the period from the end of the first year of treatment to the end of the study, using the following categories <4.0 mg/dL, ≥ 4 to <5.0 mg/dL, ≥ 5 to <6.0 mg/dL, and ≥ 6.0 mg/dL. The estimate for tophi resolution rate will be calculated for each average post-baseline sUA category using the life-table method. In calculating the percentage of subjects with tophi resolution by average post-baseline sUA, yearly intervals will be used in the life-table analysis.

13.2 Interim Analysis and Criteria for Early Termination

This study is designed to have a maximum of 624 MACE for assessing non-inferiority of febuxostat relative to allopurinol with regard to cardiovascular risk assuming a true hazard ratio of 1.0 and 90% power. Interim analyses will be conducted when approximately 25%, 50% and 75% of the events or equivalently approximately 156, 312, and 468 events have occurred, followed by a

final analysis. In this group sequential trial with 4 equally-spaced analyses and a one-sided overall significance level of 0.025, the Lan-DeMets alpha spending approach with an O'Brien-Fleming stopping boundary will be used. Therefore, at the 3 interim and at the final analyses, one-sided confidence intervals for the hazard ratio of febuxostat relative to allopurinol for the primary endpoint will be constructed using critical values obtained using the Lan-DeMets -O'Brien-Fleming alpha spending function. At each analysis, if the upper one-sided confidence limit of the hazard ratio is less than 1.3, the study will be stopped and the non-inferiority of febuxostat relative to allopurinol with regard to cardiovascular risk will be declared.

Periodically during the course of the study, a blinded assessment of the annual adjudicated MACE rate will be made. The number of subjects planned to be enrolled in this study was based on an event rate of 2.8%, which was based on limited information. Based on the overall blinded MACE rate observed, an assessment will be made to determine whether or not to adjust the number of subjects planned for enrollment.

13.3 Determination of Sample Size

A total of 7500 subjects (3750 per treatment group) are planned to be enrolled into this study. This sample size provides at least 90% power to meet a noninferiority margin of 1.3 for the hazard ratio (febuxostat relative to allopurinol) for the primary endpoint, assuming a true hazard ratio of 1.0, at a 1-sided 2.5% significance level. This study is designed to have a maximum of 624 MACE.

For the determination of noninferiority between the febuxostat treatment group and the allopurinol treatment group, the sample size calculation used the following assumptions:

- Constant proportional hazards and exponential survival curves.
- Annual adjudicated MACE rate of 2.8%.
- Maximum length of participation of 5 years.
- Accrual time of 2.5 years.
- Annual drop-out rate of 10%.

These assumptions were used prior to the initiation of the study to calculate the number of subjects to be enrolled in order to obtain the required number of MACE.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or EC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or EC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance and Regulatory Agency Audits

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#).

15.1 Regulatory Authority and IRB and/or EC Approval

IRBs and ECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or EC. If any member of the IRB or EC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or EC for the protocol’s review and approval. This protocol, the Package Insert [14], a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or EC for approval. The IRB’s or EC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug). The IRB or EC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date.

Sites must adhere to all requirements stipulated by their respective IRB or EC. This may include notification to the IRB or EC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or EC, and submission of the investigator’s final status report to IRB or EC. All IRB and EC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations ([Appendix B](#)). The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject’s personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the

requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or EC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or EC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or EC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subjects should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

CONFIDENTIAL

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the Food and Drug Administration [FDA]), the sponsor's designated auditors, and the appropriate IRBs and ECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the sponsor or the sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the investigator may publish or present the results generated at his or her site.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the sponsor's

confidential and proprietary technical information. Further, upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject participating in the study must be insured in accordance with the regulations applicable to the site where the subject is enrolled. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. Becker MA, Schumacher HR Jr, Wortmann RL, Macdonald PA, Eustace D, Palo Wa, et al. febuxostat compared with allopurinol in subjects with hyperuricemia and gout. *n engl j med* 2005;353(23):2450-61.
2. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful long-term urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol* 2009;36(6):1273-82.
3. Kim KY, Ralph Schumacher H, Hunsche E, Wertheimer AI, Kong SX. A literature review of the epidemiology and treatment of acute gout. *Clin Ther* 2003;25(6):1593-617.
4. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial *Arthritis Rheum* 2008;59(11):1540-8.
5. Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)* 2009;48(2):188-94.
6. White WB, Faich G, Borer JS, Makuch RW. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol* 2003;92(4):411-8.
7. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol*. 2004;31:2429-2432.
8. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in subjects at high risk of cardiovascular disease: A preventive cardiology information system (PreCIS) database cohort study. *Arthritis Rheum* 2008;58(2):623-630.
9. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131(1):7-13.
10. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000;283(18):2404-10.
11. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20(3):895-900.
12. ColcrysTM (colchicine) tablets Package Insert. URL Pharma, Inc. (current version).
13. Gaffo A, Schumacher HR, Saag K, Taylor W, Allison J et al. Developing American College of Rheumatology and European League against Rheumatism Criteria for definition of a flare in patients with gout. *Arthritis Rheum* 2009;Abstract 1508.

14. Uloric[®] (febuxostat) tablets Package Insert, Takeda Pharmaceuticals America, (current version).
15. Prevacid (lansoprazole) tablets Package Insert, Takeda Pharmaceuticals America (current version).
16. Naproxen tablets Package Insert, PPD [REDACTED] (current version).
17. Allopurinol tablets Package Insert, PPD [REDACTED]. (current version).

Appendix A Schedule of Study Procedures

Procedure	Screen- ing Visit	Day 1	Wk 2 (± 3 Days)	Wk 4 (±3 Days)	Wk 6 (a) (±3 Days)	Wk 8 (±3 Days)	Wk 10 (a) (±3 Days)	Mon 3 (-3 Days)	Mon 6 (±3 Days)	Mon 9 (b) (±7 Days)	Mon 12 and Every 6 Mos Until End of Study/ DoT/ET (±7 Days)	Mon 15 (b) (±7 Days)	End of Study/ DoT/ Early Termin- ation
Visit window	Day -7 to Day -1												
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Demographics	X												
Access IVRS/IWRS	X	X		X		X		X	X		X		X
Physical examination		X									X(c)		X
Medical, social, and CV history	X												
Medication history	X												
Concurrent medical conditions	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (d)	X												X
Height	X												
Tophus assessment (e)		X									X		X
Pretreatment event assessment (f)	X	X											
AE assessment (g)	X(h)	X	X	X	X	X	X	X	X	X	X	X	X
Gout flare assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessment (i)	X	X	X		X		X	X	X	X	X	X	X
Laboratory Assessment (fasting) (j)		X									X		X
12-lead ECG		X											X
Dispense study medication		X		X		X		X	X		X		
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense prophylaxis (k)	X(l)	X(m)						X					
Collect unused prophylaxis								X	X				X (n)
Collect unused study medication				X		X		X	X		X		X
Educate subject on CV events and gout flare reporting (o) and possibility of obtaining the prescription card to obtain the medication to treat gout flare (p)	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense prescription for additional gout flare medication	X												
Compliance assessment		X(l)	X	X	X	X	X	X	X	X	X	X	X
Verify subject's contact information.		X	X	X	X	X	X	X	X	X	X	X	
Follow-up contact (q)													X
Review Gout Flare Brochure		X							X				
Review Retention Program (r)		X											

Footnotes are on last table page.

- (a) Visit will occur only if the sUA ≥ 6.0 mg/dL.
- (b) Visits at Months 9 and 15 will occur only for elderly subjects (≥ 65 at the time of signing the ICF) and/or moderately renally impaired (eCLcr ≥ 30 but < 60 mL/min).
- (c) After Month 12, physical examinations will be performed annually until End of Study/DoT/Early Termination.
- (d) Weight will be measured at Screening and End of Study/DoT/Early Termination.
- (e) For those subjects with tophi present, assessments will be done at Day 1, Month 12, and annually thereafter until End of Study/DoT/Early Termination.
- (f) Collection of Pretreatment Events starts at informed consent and ends at first dose of prophylaxis or double-blind study medication, whichever comes first.
- (g) Collection of Adverse Events starts at first dose of prophylaxis or double-blind study medication, whichever comes first.
- (h) For subjects who are dispensed prophylaxis at Day -7. If not dispensed prophylaxis at Day -7, AE collection begins at Day 1.
- (i) Laboratory assessment: hematology (done only at Screening), urinalysis (done only at Screening), fasting lipid panel (done only at Day 1), INR, prothrombin and activated partial thromboplastin for subjects receiving warfarin (done at Screening and annually). Chemistry Panel 18 (at every visit): ALT, AST Albumin, Alkaline phosphatase, Total bilirubin, Total protein, Creatinine, Blood urea nitrogen, Creatine kinase, γ -Glutamyl transferase, Potassium, Sodium, Calcium, Magnesium, Glucose, Serum urate, Triglycerides, and Cholesterol.
- (j) Fasting labs required at Day 1/Randomization Visit, Month 12, and annually thereafter until End of Study/DoT/Early Termination. However, if the subject is not fasting, assessment should still be conducted.
- (k) Subjects currently on febuxostat, allopurinol, or other uricosuric agents will discontinue these medications starting at Day -7 visit and begin the washout period. Subjects are expected to remain on TDC provided open-label prophylaxis medication until the end of Month 6.
- (l) Subjects discontinuing prior ULT at Day -7.
- (m) Subjects not taking ULTs
- (n) Only when DoT or Early Termination Visit done.
- (o) Flare assessment information reported by the subject will be collected by the site personnel onto the gout flare worksheet and later transcribed to the eCRF.
- (p) The prescription card is available in the US only to treat the gout flare past Month 6 Visit for currently randomized subjects.
- (q) Subjects discontinuing study medication treatment (but have not withdrawn consent) prior to the end of study will be contacted every 2 months (± 10 days) to determine if any potential CV events have occurred. Further, sites will ask the subject if they have taken any new medications (OTC or prescription) since the last contact, or have stopped taking any ongoing medications recorded at the last contact. If yes, the generic medication name, start date, and end date will be recorded on the eCRF. Sites will also ask the subject at each contact if they have had any SAEs since the last contact. If yes, these will be recorded on the AE eCRF, and sites should follow the instructions in the Protocol Section 10.2.2, Collection and Reporting of SAEs. All SAEs should be followed up until resolution or permanent outcome of the event.
- (r) Retention Program is available in the US and Canada.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the “Statement of Investigator” (Form FDA 1572 or Site Registration Form), which must be completed and signed before the investigator may participate in this study.

In signing a Form FDA 1572 or Site Registration Form the investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
4. Secure prior approval of the study and any changes by an appropriate IRB/EC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
5. Ensure that the IRB/EC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/EC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/EC, and issue a final report within 3 months of study completion.
6. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
7. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject’s medical chart. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
8. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
9. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
10. Maintain current records of the receipt, administration, and disposition of study medication, and return all unused study medication to the sponsor.

11. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 1 working day.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The approximate number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/EC, and the monitor may inspect the records. By signing a written Informed Consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/EC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/ECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active will not be eligible for enrollment into this study. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and ECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Worksheet for All Potential Cardiovascular (CV) Events (*sample*)

Cardiovascular History

Initial _____ Follow-up _____

TO: TDC Pharmacovigilance FAX: (country specific number)

Protocol Number: _____

Investigator Name/Site Number: _____ Subject No/Initials: _____

Adverse Event (diagnosis): _____

Brief description of cardiovascular event:

When applicable, please provide the following for all events:

- ☐ Pertinent laboratory results (with reference lab values), imaging and cardiac testing reports
- ☐ Hospital admission notes and relevant hospital records related to the event
- ☐ Surgical, consultant and pathology reports
- ☐ Hospital discharge summary

If a potential MI event (eg, MI, Chest Pain, Silent MI, ECG Changes, Ischemia, Shortness of Breath)

- ☐ Cardiac enzymes (CPK-MB and/or troponin with reference values)
- ☐ ECG (pre-treatment and related documentation)
- ☐ Description of clinical signs and symptoms
- ☐ Cardiology consultation notes

If a potential STROKE event (eg, Ischemic Stroke, Cerebral Hemorrhage, TIA)

- ☐ CT or MRI images and results
- ☐ Other relevant tests and duration of neurological signs and symptoms
- ☐ Description of neurologic signs and symptoms
- ☐ Neurology consultation notes

If a potential ANGINA event (eg, Unstable Angina, Chest Pain)

- ☐ Cardiac biomarkers with reference ranges
- ☐ ECG (pretreatment and all other tracings related to the event)
- ☐ Other relevant tests (stress tests, cardiac catheterization) and duration of symptoms of ischemia
- ☐ Coronary revascularization procedure records

Protocol Number: _____

Investigator Name/Site Number: _____ Subject No/Initials: _____

If a potential CORONARY REVASCULARIZATION (eg, Angioplasty or Coronary Bypass Graft surgery)

☐ Coronary revascularization procedure records

If a potential CEREBRAL REVASCULARIZATION

☐ Revascularization procedure records

If a potential VENOUS AND PERIPHERAL ARTERIAL VASCULAR THROMBOTIC event (eg, Pulmonary Embolism, DVT, Thrombosis, Ischemia)

☐ Evidence of embolism (eg, CT angiography)

☐ Evidence of occlusion (eg, Doppler studies)

If a potential CONGESTIVE HEART FAILURE event (eg, Dyspnea, Shortness of Breath, Pulmonary Edema)

☐ Physical examination and auscultatory findings

☐ Radiographic documentation

☐ Echocardiographic documentation

☐ Cardiology Consultation Notes with documentation of parenteral therapy

If a potential ARRYTHMIA event (eg, atrial fibrillation, ventricular tachycardia)

☐ Pre-treatment ECG and all other ECGs related to the event

☐ Clinical history

Other relevant hospital records (please list):

Investigator Signature _____ Date _____

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Appendix F Rash Adverse Event Worksheet (sample)

Rash Adverse Event Worksheet

Investigator Name/Number: _____ Protocol Number: TMX_67-_____
Subject Initials/Number: _____ Date of Subject Contact: _____
Date of Onset: _____ End Date: _____
Description of Rash (check all that apply):

- ☐ ERYTHEMATOUS
☐ BULLOUS
☐ EXFOLIATIVE
☐ CONTACT DERMATITIS

- ☐ MACULAR
☐ PAPULAR
☐ VESICULAR
☐ OTHER (specify): _____

Location (check all that applies):

- ☐ TRUNK ☐ FACE ☐ NECK EXTREMITIES →

Study medications Discontinued → ☐ Yes ☐ No

Concurrent Medication: List Medication(s)

Medication	Dose	Units	Freq.	Route	Start/Stop Date	Reason for Use
/						
/						

Medication Used To Treat → ☐ Yes ☐ No

If Yes List Medication(s)

Medication	Dose	Freq.	Route	Start/Stop Date	Was this effective?
/					
/					

Laboratory Test Done? → ☐ Yes ☐ No

If Yes, which one:

- ☐ CBC
☐ CHEMISTRY

- ☐ PLATELET
☐ OTHER:

Physician assessment of the likelihood that this episode is related to blinded study medication:

- ☐ YES
☐ NO

Signature of Person Completing Assessment

Date

This form must be completed and faxed to TDC within 48 hours of site knowledge of the event:

Attention: Rash Worksheet Coordinator
FAX number: (country specific number)

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Protocol Number: TMX-67 _____
Investigator Name/Number: _____
Subject Initials/Number: _____

PHYSICIAN ASSESSMENT

Was additional medication prescribed to treat the gout flare?

☐ Yes: ☐ No
Medication Name: _____
Dose _____ Freq. _____ Route _____

Physician assessment of the likelihood that this episode is a true gout attack:

☐ Definitely
☐ Probably
☐ Possibly: Alternative etiology: _____
☐ Probably Not: Alternative etiology: _____

Date of Full Resolution of Flare: _____

Comments:

Signature of Investigator

Date

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Gout Flare Assessment Worksheet (continued)

Guideline for assessing signs and symptoms:

Tenderness

- | | |
|----------|-------------------------|
| Mild | - subject states tender |
| Moderate | - subject winces |
| Severe | - subject withdraws |

Swelling

- | | |
|----------|---------------------------------|
| Mild | - just detectable |
| Moderate | - obvious swelling of the joint |
| Severe | - swelling beyond the joint |

Warmth

- | | |
|----------|--|
| Mild | - detectable compared to contralateral joint |
| Moderate | - obviously warmer |
| Severe | - Hot |

Redness

- | | |
|----------|--|
| Mild | - slightly darker than contralateral joint |
| Moderate | - obviously darker |
| Severe | - bright red |

Appendix H Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 6.

Pages 1, 2, 11, 16, 17, 19, 40, 86, 92, 94

Universal update to protocol to update the name of the Sponsor from Takeda Global Research & Development Center, Inc. (TGRD) to Takeda Development Center Americas, Inc. (TDC).

Page 2, Section 1.1 Contacts

Existing Text

Medical monitor (medical advice on protocol, compound and medical management of subjects)
Responsible medical officer (carries overall responsibility for conduct of study)

PPD

Revised Text

Medical monitor (medical advice on protocol, compound and medical management of subjects)

PPD

Responsible medical officer (carries overall responsibility for conduct of study)

Rationale for Amendment

Update to Contacts to reflect change in Medical Monitor and Responsible Medical Officer, and the addition of a backup Medical Monitor.

Page 3, Section 1.2 Approval

Existing Text

PPD

Date

PPD

Date

Revised Text

PPD

Date

PPD

Date

Rationale for Amendment

Update to reflect change in Medical Director and Clinical Study Manager.

Page 11, Section 2.0 Study Summary, Study Design

Page 25, Section 6.1 Study Design

Page 30, Section 6.2 Justification for Study Design, Dose, and Endpoints

Page 56, Section 9.3 Schedule of Observations and Procedures

Existing Text

The length of the study is expected to be approximately 5 years.

Revised Text

The length of the study is expected to be approximately **9** years.

Rationale for Amendment

Slower than expected enrollment duration has extended the overall length of the study.

Page 12, Section 2.0 Study Summary, Study Design

Page 26, Section 6.1 Study Design

Page 86, Appendix A Schedule of Study Procedures, footnote (b)

Existing Text

In addition, subjects with moderate renal impairment (eCLcr <60 mL/min) and/or subjects...

Revised Text

In addition, subjects with moderate renal impairment (eCLcr **≥30 but** <60 mL/min) and/or subjects...

Rationale for Amendment

Clarification to creatine clearance criteria that includes the lower acceptable bound as determined by study exclusion criteria.

Page 12, Section 2.0 Study Summary, Study Design

Page 72, Section 11.2 CV Endpoints Committee

Existing Text

An Independent Cardiovascular (CV) Endpoints Committee will prospectively review all suspected CV events using blinded data. All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV AEs.

Revised Text

An Independent Cardiovascular (CV) Endpoints Committee will prospectively review all suspected **serious** CV events using blinded data. All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV SAEs.

Rationale for Amendment

Non-serious adverse events are not likely to be adjudicated to a MACE endpoint and the FDA agreed to remove the requirement for adjudication of non-serious events.

Page 12, Section 2.0 Study Summary, Study Design

Page 26, Section 6.1 Study Design

Page 87, Appendix A Schedule of Study Procedures, footnote (q)

Existing Text

Subjects who are withdrawn from study medication treatment but have not withdrawn consent will be *followed* for the duration of the study or until the subject experiences a CV event that is positively adjudicated as a MACE *via phone calls every 2 months*.

Revised Text

Subjects who are withdrawn from study medication treatment but have not withdrawn consent will be **contacted every 2 months** for the duration of the study or until the subject experiences a CV event that is positively adjudicated as a MACE.

Rationale for Amendment

Renamed follow-up contact procedure to indicate flexibility in method of contacting subjects.

Page 13, Section 2.0 Study Summary, Duration of Treatment

Existing Text

[T]he maximum length of participation is expected to be approximately 5 years.

Revised Text

[T]he maximum length of participation is expected to be approximately **9** years.

Rationale for Amendment

Slower than expected enrollment duration has extended the overall length of the study.

Page 13, Section 2.0 Study Summary, Period of Evaluation

Existing Text

Maximum of 5 years treatment duration.

Revised Text

Maximum of **9** years treatment duration.

Rationale for Amendment

Slower than expected enrollment duration has extended the overall length of the study.

Page 15, Section 2.0 Study Summary, Sample Size Justification

Page 77, Section 13.3 Determination of Sample Size

Added Text

These assumptions were used prior to the initiation of the study to calculate the number of subjects to be enrolled in order to obtain the required number of MACE.

Rationale for Amendment

To clarify the observed information from the ongoing study may no longer be consistent with the assumptions used to calculate sample size.

Page 16, Section 3.1 Study-Related Responsibilities

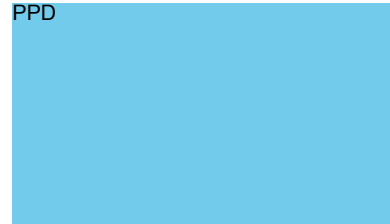
Added Text

Clinical supply return

PPD



PPD



Rationale for Amendment

Updated to include additional clinical trial material return facility.

Page 27, Section 6.1 Study Design

Existing Text

All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV AEs.

Revised Text

All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths and potential CV SAEs.

Rationale for Amendment

Non-serious adverse events are not likely to be adjudicated to a MACE endpoint and the FDA agreed to remove the requirement for adjudication of non-serious events.

Page 28, Figure 6.a

Page 34, Section 7.3.2 Excluded Medications and Treatments

Page 46, Section 8.5 Unblinding

Page 48, Section 9.1.3 Physical Examination Procedure

Page 49, Section 9.1.4 Weight and Height Procedure

Page 49, Section 9.1.6 Documentation of Concomitant Medications

Page 51, Section 9.1.10 ECG Procedure

Page 54, Section 9.1.17 Physical Assessment of Tophi

Page 85, Appendix A Schedule of Study Procedures, table and footnotes

Existing Text

Final Visit/End of Treatment/Early Termination Visit

Revised Text

End of Study/Discontinuation of Treatment/Early Termination Visit

Rationale for Amendment

Revised visit name to more accurately reflect the purpose and procedures being performed; and to delineate the differences between the three visit types.

Page 32, Section 7.1 Inclusion Criteria

Added Text

5. The subjects must have either:

- a sUA level ≥ 7.0 mg/dL (≥ 416 $\mu\text{mol/L}$) at the Screening Visit **OR**
- a sUA level ≥ 6.0 mg/dL (≥ 354 $\mu\text{mol/L}$) at the Screening Visit **AND** inadequately controlled gout (≥ 1 flare in the 12 months prior to screening and/or the presence of tophi).

Rationale for Amendment

Added International System of Units (SI) to aid ex-US sites, who are more familiar with, and tend to maintain patient records in SI units, in quickly and accurately determining entry criteria for serum uric acid levels.

Page 34, Section 7.3 Required Medications and Treatments

Existing Text

Subjects randomized to allopurinol, with normal renal function or mild renal impairment (eCLcr ≥ 30 but ≥ 60 mL/min) will initially receive allopurinol 300 mg QD with the dose increased in 100 mg increments monthly until either a sUA < 6.0 mg/dL or a maximum allopurinol dose of 600 mg QD is achieved.

Revised Text

Subjects randomized to allopurinol, with normal renal function or mild renal impairment (eCLcr ≥ 60 mL/min) will initially receive allopurinol 300 mg QD with the dose increased in 100 mg

increments monthly until either a sUA <6.0 mg/dL or a maximum allopurinol dose of 600 mg QD is achieved.

Rationale for Amendment

Removed eCLcr ≥ 30 mL/min as this was not the correct range for normal or mild renal impairment.

Page 37, Section 7.4 Procedures for Discontinuation from the Study Drug Treatment with Continued Participation in the Study via Follow-up Contacts

Existing Text

(Section 7.4)

Subjects who discontinue study drug treatment will continue to participate in the study through Telephone Contacts unless consent is withdrawn by the subject or until the subject experiences a CV event that is positively adjudicated as a MACE.

The primary reason for permanent discontinuation of study drug treatment should be noted using the following categories:

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

NOTE: Subjects who experience ALT or AST $>3 \times \text{ULN}$ in conjunction with elevated total bilirubin $>2 \times \text{ULN}$ and satisfy the following 2 criteria: (1) The liver injury is hepatocellular in nature and there is not a prominent cholestatic component, or (2) there is no more likely alternative cause than drug induced liver injury, such as acute viral hepatitis A or B, or other acute liver disease, should be permanently discontinued from the study drug treatment.

2. Major protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from taking study drug treatment. The reason for withdrawal, if provided, should be recorded in the eCRF.

NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.

4. Pregnancy. The subject is found to be pregnant
5. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented. Before a subject is considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within 4 weeks of the most recently missed study visit must be sent in an effort to contact the subject.
6. Study termination. The sponsor, IRB, ethics committee (EC), or regulatory agency terminates the study.

7. Other. The specific reasons should be recorded in the “specify” field of the eCRF.

The primary reason that the subject prematurely discontinued study drug should be listed on the End of Study Drug page of the eCRF. End of Study Drug eCRF should be completed when the subject discontinues study medication or completes the full cycle of study medication; end of Study Drug eCRF completion is independent of the decision to continue participation in the study via *telephone* contacts.

Efforts will be made to avoid any subject being lost to follow-up during the conduct of the study. Investigators should refer to Section 9.0 for gout flare assessment and Section 9.1.15 for gout flare treatment.

(Section 7.5)

Subjects who stop taking study medication will continue in the study as long as consent is not withdrawn by the subject until the subject experiences a CV event that is positively adjudicated as a MACE, the required number of study MACE events have occurred, or until the study concludes. The contacts will occur via phone calls every 2 months.

In addition, efforts should be made to perform all procedures required as part of the Early Termination Visit when the subject discontinues study drug treatment, regardless of whether or not the subject continues participation in the study.

Further, at each *telephone* contact, sites will ask the subject if they have taken any new medications (OTC or Prescription) since the last contact, or have stopped taking any ongoing medications recorded at the last contact. If yes, the generic medication name, start date, and end date and reason for use will be recorded on the eCRF.

Sites will also ask the subject at each *telephone* contact if they have had any SAEs or any potential cardiovascular adverse events since the last *telephone* contact. If yes, these will be recorded on the AE eCRF, and sites should follow the instructions in the Protocol Section 10.2.2, Collection and Reporting of SAEs if applicable. All SAEs should be followed up until resolution or permanent outcome of the event.

Subjects who have withdrawn from study medication treatment but have not withdrawn consent will be followed until the subject experiences a CV event that is positively adjudicated as a MACE or until the study concludes. Subjects will be contacted by telephone every 2 months (± 10 days) to determine if any potential CV events have occurred.

If the subject has had a potential CV event, he/she should bring the event related documents (labs, hospital discharge summary, etc) to the clinic.

If after two telephone attempts a subject cannot be reached, then the subject's emergency person will be contacted. Before a subject is considered lost to follow-up, a minimum of two documented telephone contact attempts must have been made and 1 certified letter must have been sent within 4 weeks of the most recently missed telephone call to the subject or emergency contact in an effort to contact the subject.

Revised Text

Subjects who discontinue study drug treatment will continue to participate in the study through **follow-up** contacts unless: consent is withdrawn by the subject; the subject experiences a CV event that is positively adjudicated as a MACE (**the study team will notify the site in writing when it is no longer necessary to follow the subject with a positive MACE adjudication**); the **required number of study MACE events have occurred**; or **until the study is ended**. **Follow-up contacts will occur every 2 months (±10 days).**

The primary reason for permanent discontinuation of study drug treatment should be noted using the following categories:

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

NOTE: Subjects who experience ALT or AST >3xULN in conjunction with elevated total bilirubin >2xULN and satisfy the following 2 criteria: (1) The liver injury is hepatocellular in nature and there is not a prominent cholestatic component, or (2) there is no more likely alternative cause than drug induced liver injury, such as acute viral hepatitis A or B, or other acute liver disease, should be permanently discontinued from the study drug treatment.

2. Major protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from taking study drug treatment. The reason for withdrawal, if provided, should be recorded in the eCRF.

NOTE: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.

4. Pregnancy. The subject is found to be pregnant
5. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
6. Study termination. The sponsor, IRB, ethics committee (EC), or regulatory agency terminates the study.
7. Other. The specific reasons should be recorded in the "specify" field of the eCRF.

The primary reason that the subject prematurely discontinued study drug should be listed on the End of Study Drug page of the eCRF. End of Study Drug eCRF should be completed when the subject discontinues study medication or completes the full cycle of study medication; end of Study Drug eCRF completion is independent of the decision to continue participation in the study via **follow-up** contacts.

These subjects should undergo all procedures required as part of the Discontinuation of Treatment Visit when the subject stops study drug treatment. In the event that these subjects later withdraw consent from participation in the study, an additional final Early Termination visit does not need to be performed.

At each **follow-up** contact, sites will ask the subject if they have taken any new medications (over the counter or prescription) since the last contact, or have stopped taking any ongoing medications recorded at the last contact. If yes, the generic medication name, start date, and end date and reason for use will be recorded on the Medication Information Obtained During **Follow-up** Contact eCRF.

Sites will also ask the subject at each **follow-up** contact if they have had any serious adverse events (SAEs) or any potential cardiovascular adverse events since the last contact. If yes, these will be recorded on the AE eCRF, and sites should follow the instructions in the Protocol Section 10.2.2, Collection and Reporting of SAEs if applicable. All SAEs should be followed up until resolution or permanent outcome of the event.

If the subject has had a potential serious CV event, he/she should bring the event related documents (labs, hospital discharge summary, etc) to the clinic. **The study team will notify the site in writing upon a positive MACE adjudication when it is no longer necessary to follow a subject.**

Efforts will be made to prevent any subject being lost to follow-up during the conduct of the study. Investigators should refer to Section 9.0 for gout flare assessment and Section 9.1.15 for gout flare treatment. Before a subject is considered lost to follow-up, a minimum of two documented telephone contact attempts must have been made and one certified letter must have been sent within 4 weeks of the most recently missed telephone call to the subject and/or emergency contact in an effort to contact the subject.

Rationale for Amendment

Combined two sections (7.4 and 7.5) from previous protocol version to clarify and aid in proper protocol for DoT subjects; which includes adding all instances where a DoT subject will no longer be followed. Clarify the expectations for attempted contacts with subjects who are lost to follow-up. Renamed follow-up contact procedure to indicate flexibility in method of contacting subjects.

Page 38, Section 7.5 Procedures for Early Termination of a Subject from the Study (Both Drug and Visits)

Existing Text

A subject's study medication may be temporarily suspended or permanently ceased at any time at the discretion of the Investigator.

If consent is withdrawn for continued participation (ie, bimonthly phone calls) after discontinuing study medication treatment, the primary reason for discontinuation of study participation should be noted using the following categories:

1. Adverse Event. The subject experiences a CV event that is positively adjudicated as a MACE.

Revised Text

A subject may discontinue his or her participation from the study without giving a reason at any time during the study. In addition, efforts should be made to perform all procedures required as part of the Early Termination Visit, even if the subject withdrew consent.

The primary reason for discontinuation of study participation should be noted using the following categories:

1. Adverse Event. **A subject taking study medication has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the event. Also applies to subjects no longer taking study medication who are in follow-up who experience a serious CV event that is positively adjudicated as a MACE.**
NOTE: this reason is not intended to be selected for subjects in follow-up experiencing non-MACE AEs as these subjects can, and should, continue participation.

Rationale for Amendment

Updated section title to more accurately reflect the content of the section. Corrected language around early termination due to AEs. Renamed follow-up contact procedure to indicate flexibility in method of contacting subjects.

Page 40, Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling **Page 44, Section 8.1.3 Dose and Regimen**

Existing Text

Colchicine 0.6 mg tablets ^{PPD} [REDACTED] or URL Pharma, Inc. / Mutual Pharmaceutical Company, Inc., Philadelphia, PA) will be supplied in child resistant bottles containing 100 tablets each.

Naproxen (West-ward Pharmaceutical Corp., Eatontown, NJ) will be supplied in child resistant bottles with 100 tablets, each tablet containing 250 mg of naproxen.

Revised Text

Colchicine 0.6 mg tablets ^{PPD} [REDACTED] or **Takeda Pharmaceuticals America, Deerfield, IL [formerly URL Pharma, Inc. / Mutual Pharmaceutical Company, Inc., Philadelphia, PA]** will be supplied in child resistant bottles containing 100 tablets each.

Naproxen (^{PPD} [REDACTED] or ^{PPD} [REDACTED] ^{PPD} [REDACTED] **India**) will be supplied in child resistant bottles with 100 tablets, each tablet containing 250 mg of naproxen.

Rationale for Amendment

To reflect most recent manufacturing information.

Page 46, Section 8.5 Unblinding Procedure

Page 86, Appendix A Schedule of Study Procedures

Existing Text

Telephone Contact

Revised Text

Follow-up contact

Rationale for Amendment

Renamed follow-up contact procedure to indicate flexibility in method of contacting subjects.

Page 46, Section 8.5 Unblinding Procedure

Added Text

For unblinding a subject, the investigational drug blind can be obtained by accessing the IVRS.
Please refer to IVRS Unblinding Worksheet packet.

Rationale for Amendment

Added text to offer further guidance for finding instructions on how to unblind a subject in IVRS.

Page 49, Section 9.1.6 Documentation of Concomitant Medications

Added Text

Changes in medication for subjects that have discontinued treatment but remain in follow-up should be recorded on the Medication Information Obtained During Follow-up Contact eCRF, and not on the Concomitant Medications eCRF.

Rationale for Amendment

Provide further clarification and reminder to users about where to properly record concomitant medication information collected during follow-up contact calls. Renamed follow-up contact procedure to indicate flexibility in method of contacting subjects.

Page 50, Table 9.a footnotes

Existing Text

(c) Lipid panel *fasting* at Day 1, *Months 12/24/36/48 & Final Visit/ET/EoT only*.

Revised Text

(c) Lipid panel **only** at Day 1.

Rationale

Correction to protocol discrepancy whereas lipid panel testing was noted in Table 9.a as performed at Day 1 and then annually thereafter, but Appendix A noted the panel as being done at Day 1 only. Because the contracted central laboratory was only performing testing as designated in Appendix

A, this lipid panel was not being conducted for any subjects beyond Day 1, and it was determined that the appropriate correction was to maintain this schedule.

Page 53, Section 9.1.14 Gout Flare Prophylaxis

Added Text

Prophylaxis medication is only provided until the Month 6 visit, but upon the Investigator's request, continued prescription may be allowed. Please note that study prescription cards intended to pay for acute gout flare medication cannot be used to pay for ongoing prophylaxis medication.

Rationale for Amendment

Provided further instruction and clarification around proper use of the study prescription card due to extensive questions from clinical sites about its use.

Page 56, Section 9.3.1 Screening

Existing Text

Please contact the Sponsor, if randomization does not occur within four weeks of the Screening visit. Screening may be less than 7 days for subjects not washing off of ULTs. Screening period may be longer than 7 days depending on whether subject has a flare or requires a repeat sUA test.

Revised Text

Please contact the **Medical Monitor** if randomization does not occur within four weeks of the Screening visit. Screening may be less than 7 days for subjects not washing off of ULTs. Screening period may be **up to 28 days** depending on whether subject has a flare or requires a repeat sUA test.

Rationale for Amendment

To correct who is the proper person to contact with these communications; also further clarifies the parameters within which a repeat screening visit is allowed to be conducted.

Page 58, Section 9.3.2 Study Randomization

Added Text

- Review the Retention Program (subjects in the US and Canada only). **Unless subjects opt-out, enroll them in the program.**
- **Review the Gout Flare brochure.**

Rationale for Amendment

Added text around the procedures for review of the retention program to emphasize the importance of enrolling subjects in the program, if possible. Added a bulleted study procedure to remind sites of the need for review of gout flare brochure to further subject education around flares.

Page 60, Section 9.3.3 Treatment Phase

Existing Text

9.3.3.6 Month 3 (-3 Days)

Revised Text

9.3.3.6 Month 3 (± 3 Days)

Rationale for Amendment

Correct visit range typographical error.

Page 61, Section 9.3.3 Treatment Phase

Existing Text

9.3.3.7 Months 6 (± 3 Days), 12, 18, 24, 30, 36, 42 48 and 54 (± 7 Days)

- Call IVRS/IWRS and dispense assigned study medication with dosing instruction.
- Physical examination (Months 12, 24, 36 and 48).
- Vital signs.
- Tophus Assessment (Months 12, 24, 36 and 48).
- AE assessment.
- Gout flare assessment.
- Laboratory assessment (fasting, if at all possible on Months 12, 24, 36, and 48).
- Concomitant medication assessment.
- Collect unused prophylaxis medication and assess compliance (Month 6).
- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares and possibility of obtaining the prescription card to obtain medication to treat gout flares (only in the US).
- Verify subject's contact information (including details of emergency contact).

Revised Text

9.3.3.7 Month 6 (± 3 Days)

- Access IVRS/IWRS and dispense assigned study medication with dosing instruction.
- Vital signs.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.

- Concomitant medication assessment.
- Collect unused prophylaxis medication and assess compliance.
- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares and possibility of obtaining the prescription card to obtain medication to treat gout flares (only in the US).
- Verify subject's contact information (including details of emergency contact).
- **Review the Retention Program (subjects in the US and Canada only).**
- **Review the Gout Flare Brochure.**

9.3.3.9 Month 12 and Every 6 Months Until End of Study/Discontinuation of Treatment/Early Termination (± 7 Days)

- Access IVRS/IWRS and dispense assigned study medication with dosing instruction.
- Physical examination (performed annually).
- Vital signs.
- Tophus Assessment (performed annually for subjects with tophi present).
- AE assessment.
- Gout flare assessment.
- Laboratory assessments (fasting if at all possible, however if the subject is not fasting continue with visit).
- Concomitant medication assessment.
- Collect unused study medication and assess compliance.
- Educate subject on reporting of potential CV events and gout flares and possibility of obtaining the prescription card to obtain medication to treat gout flares (only in the US).
- Verify subject's contact information (including details of emergency contact).

Rationale for Amendment

Split existing section up (into Section 9.3.3.7 and 9.3.3.9) to more clearly define the procedures to be completed at the Month 6 visit versus visits from Month 12 onwards. Removed reference to specific visit months because subject participation will vary due to the endpoint nature of the study. Added review of the retention program and gout flare brochure as reminders to conduct those procedures at Month 6.

Page 62, Section 9.3.3 Treatment Phase

Existing Text

9.3.3.9 End of Study Treatment

Subjects who have withdrawn from study medication treatment but have not withdrawn consent will continue to be followed. Subjects will be contacted by telephone every 2 months (± 10 days) to determine if any potential CV events have occurred (see Section 7.5 for telephone contact details). If the subject has had a potential CV event, he/she should bring the event related documents (labs, hospital discharge summary, etc) to the clinic. If after two attempts a subject cannot be reached then the subject's emergency person will be contacted. Before a subject is considered lost to follow-up, a minimum of two documented telephone contact attempts must have been made and 1 certified letter must have been sent within 4 weeks of the most recently missed telephone call in an effort to contact the subject. Subjects who prematurely discontinue from the study and experience a CV event that is positively adjudicated as a MACE will no longer be followed. Further, at each telephone contact, sites will ask the subject if they have taken any new medications (OTC or Prescription) since the last contact, or have stopped taking any ongoing medications recorded at the last contact. If yes, the generic medication name, start date, end date and reason for use will be recorded on the eCRF.

Sites will also ask the subject at each telephone contact if they have had any SAEs or any potential cardiovascular adverse events since the last telephone contact. If yes, these will be recorded on the AE eCRF, and sites should follow the instructions in the Protocol Section 10.2.2, Collection and Reporting of SAEs if applicable. All SAEs should be followed up until resolution or permanent outcome of the event.

9.3.3.10 Month 60 Final Visit/End of Treatment or Early Termination

The following procedures will be performed and documented at the Final Visit/End of Treatment or Early Termination Visit.

- Call IVRS/IWRS to complete the subject or for Early Termination.
- Physical examination.
- Vital signs.
- Weight.
- Tophus assessment.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments.
- 12-lead ECG.
- Concomitant medication assessment.

- Collect unused study medication and assess compliance.
- Collect unused prophylaxis medication (*EoT or Early Termination*).

For all subjects receiving any Sponsor supplied medication, the investigator must complete both the End of Study Drug CRF page and the End of Study Visit eCRF page.

Revised Text

9.3.3.10 End of Study/Discontinuation of Treatment/Early Termination

All efforts should be made to prevent any subject being lost to follow-up during the conduct of the study.

Subjects who either discontinue study drug treatment, or who fully withdraw consent, should complete the following procedures at their Discontinuation of Treatment Visit or Early Termination Visit, respectively. For subjects who are active in the study (taking study medication) at the time the independent CV Endpoints Committee determines that the targeted number of adjudicated MACE have been reached, instructions will be provided by the Sponsor regarding the scheduling of the End of Study Visit, which includes the following procedures.

- Access IVRS/IWRS to complete the subject or for Early Termination.
- Physical examination.
- Vital signs.
- Weight.
- Tophus assessment.
- AE assessment.
- Gout flare assessment.
- Laboratory assessments (**fasting if at all possible, however if the subject is not fasting continue with visit**).
- 12-lead ECG.
- Concomitant medication assessment.
- Collect unused study medication and assess compliance.
- Collect unused prophylaxis medication (**if applicable**).

For all subjects receiving any Sponsor supplied medication, the investigator must complete both the End of Study Drug eCRF page and the End of Study Visit eCRF page.

Rationale for Amendment

Removed text redundant with other sections. Revised visit name and section text to more accurately reflect the purpose and procedures being performed; and to delineate the differences

between the three visit types. Added instruction around subjects who are active in the study at the time that the last MACE is adjudicated. Included a reminder instruction around requirements for fasting at the final visit. Added text to clarify when drug return is not applicable.

Page 71, Section 10.2.5 Evaluation of CV Safety

Existing Text

Each death, all CV serious adverse events and selected non-serious adverse events which are considered by the investigator to be potentially of cardiovascular nature, including any medically significant updates, will be sent by Takeda to a blinded CV Endpoints committee (see Section 11.2) for adjudication. Potential non-serious (non-hospitalized) cardiovascular adverse events may include, but are not limited to, events such as chest pain, angina, dyspnea/shortness of breath, arrhythmias, and syncope.

All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths, all SAEs and selected nonserious events that are considered by the investigator to be potentially of CV nature. The adjudication committee may also identify additional events for adjudication through periodic data review. A CV worksheet will be provided to the investigational sites as a guide to ensure that supporting clinical information for each of these events are collected and compiled by the site and forwarded by fax or mail to Takeda Pharmacovigilance when available. The worksheet is not intended to be all inclusive and investigators should use medical judgment to determine what additional supporting documentation should be collected.

Revised Text

Each death and selected serious **cardiovascular** adverse events, including any medically significant updates, will be sent by Takeda to a blinded CV Endpoints committee (see Section 11.2) for adjudication. **The final selection of the CV events for adjudication is done by the adjudication committee chair. Non-serious, potential CV events will not be adjudicated.**

All investigational sites will be required to collect relevant clinical information required for adjudication of all deaths **and selected CV SAEs**. A CV worksheet will be provided to the investigational sites as a guide to ensure that supporting clinical information for each of these events are collected and compiled by the site and forwarded to Takeda Pharmacovigilance when available. The worksheet is not intended to be all inclusive and investigators should use medical judgment to determine what additional supporting documentation should be collected.

Rationale for Amendment

Clarified the adjudication process, deleted requirement for adjudication of non-serious events. Non-serious adverse events are not likely to be adjudicated to a MACE endpoint and the FDA agreed to remove the requirement for adjudication of non-serious events.

Page 75, Section 13.1.3 Safety Analyses

Existing Text

A blinded CV Endpoints Committee will adjudicate each death and major cardiovascular adverse event to determine if it meets the MACE criteria.

Revised Text

A blinded CV Endpoints Committee will adjudicate each death and **selected serious** cardiovascular adverse event to determine if **the event** meets the MACE criteria.

Rationale for Amendment

Non-serious adverse events are not likely to be adjudicated to a MACE endpoint and the FDA agreed to remove the requirement for adjudication of non-serious events.

Page 85, Appendix A Schedule of Study Procedures

Added Text

Review Gout Flare Brochure		X						X				
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Rationale for Amendment

Included as a reminder to sites to formally perform a review of the gout flare information with all subjects.

Page 86, Appendix A Schedule of Study Procedures, footnotes

Existing Text

(b) For those subjects with tophi present, assessments will be done at Day 1, Month 12, 24, 36, 48 and Final Visit/ EoT or Early Termination.

(f) Fasting labs required at Day 1/Randomization Visit, Month 12, 24, 36, 48 and Final Visit/ EoT or Early Termination.

(i) EoT will have procedures as at Month 60 visit.

Revised Text

(e) For those subjects with tophi present, assessments will be done at Day 1, Month 12, **and annually thereafter until End of Study/DoT/Early Termination.**

(j) Fasting labs required at Day 1/Randomization Visit, Month 12, **and annually thereafter until End of Study/DoT/Early Termination. However, if the subject is not fasting, assessment should still be conducted.**

Rationale for Amendment

All footnote numbering was updated to facilitate easier flow and reference within the table. Footnotes regarding tophi and laboratory assessments were updated to remove reference to specific visit months because subject participation will vary due to the endpoint nature of the study; also added reminder instruction around the necessity for fasting during laboratory assessment visits. Removed unnecessary and potentially confusing footnote appended to the End of Study/DoT/Early Termination visit.

Amendment 6 – A Multicenter, Randomized, Active-Control, Phase 3B Study to Evaluate
the Cardiovascular Safety of Febuxostat and Allopurinol in Subjects with Gout and
Cardiovascular Comorbidities

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Operations Approval	28-Aug-2013 14:28
	Pharmacovigilance Approval	28-Aug-2013 15:13
	Biostatistics Approval	28-Aug-2013 15:19
	Clinical Operations Approval	28-Aug-2013 15:22
	Clinical Science Approval	28-Aug-2013 15:33

1.3 Protocol Amendment TMX-67_301.001

This document describes changes in reference to Protocol TMX-67_301.001, dated 20 January 2010. Please note that this amendment includes major changes to the overall study design and conduct of the study; therefore only an overview of the changes is provided in this section.

Change in Protocol	Rationale
Secondary Efficacy Endpoints Moved to Additional Endpoints	Since the majority of subjects will receive ULT that will decrease sUA <6.0 mg/dL, differences between treatment groups are no longer a relevant secondary endpoint
Removed ECGs from Safety Assessments	ECGs will be performed at the Screening Visit and per the investigator's discretion should a cardiovascular event occur
Study Duration Changed to Approximately 5 Years and the Number of Subjects Increased to 7500	Complete event-driven trial in a shorter period of time
Change enrollment criteria to include subjects with (1) a serum urate level (sUA) ≥ 7 mg/dL or (2) with a sUA ≥ 6 mg/dL AND at least one flare in the 12 months prior to screening and/or the presence of tophi	Increase participation of gout subjects in safety study that may not have otherwise qualified due to sUA levels
Shortened washout period for prior urate lowering therapy to 7 days from 14 days	To make washout period consistent with duration appropriate for drug clearance and not to achieve hyperuricemic state
Introduce allopurinol titration (in 100 mg increments) based on sUA response to a maximum of 400 mg in subjects with moderate renal impairment and 600 mg in normal/mild renal impairment subjects (NOTE: Additional visits have been added at Weeks 6, 8 and 10 to monitor sUA response for those subjects who do not achieve sUA <6.0 mg/dL at the previous visit.)	Prevent subjects randomized to allopurinol from withdrawing from the study due to inadequate sUA response

Change in Protocol	Rationale
Investigator and sponsor will be unblinded to sUA levels until Week 12 visit (NOTE: both parties will remain blinded to study treatment.)	Assist in ensuring that subjects are titrated to a dose of study treatment that will maintain sUA <6.0 mg/dL for the 5 year study duration
Updated entry criteria for females to be ≥ 55 years of age and removed requirement for FSH testing	Women over age 55 are post-menopausal and confirmation via laboratory testing is not required
Updated protocol to remove any restrictions related to thiazide diuretic use	Any required allopurinol titration will occur in 100 mg increments and subjects will be monitored every 6 months during the course of the study
Revised Study Medication and Treatment Section due to inclusion of higher allopurinol doses and addition of placebo capsules	To maintain blinding, all subjects will be required to take 2 capsules of study medication daily
Updated schedule of events to reflect yearly physical exams	To follow typical clinical practice
Updated criteria for causality of adverse events	Align with company policy to utilize Yes or No response
Updated proposed CV event rate to 2.8%	Limited available information on true CV rate in high risk populations
Updated colchicine dosing recommendations for acute gout flares	Recently approved US labeling providing specific guidance regarding colchicine dosing
Deleted thyroid, and hs-crp	To streamline the study conduct; hematology and urinalysis will be done at screening and chemistry (including liver function tests) will be done at screening and at least every 6 months during the study
Added additional visits at Month 9 and Month 15 for elderly subjects and subjects with moderate renal impairment	To more frequently monitor LFTs and renal function in elderly subjects and subjects with moderate renal impairment
Removed the telephone contacts every 2 months after Month 12 visit for subjects still receiving study medication	Subjects will be seen in the clinic at least every 6 months; telephone contacts will still be made every 2 months for subjects who have discontinued study medication but are being followed for potential CV events.

Change in Protocol	Rationale
Clarified that detailed information on aspirin and NSAID use will be collected and specified how the analyses will account for use of these medications	Use of these medications could potentially confound the interpretation of study events
Specified details of signs and symptoms to be collected for gout flares	To apply the standardized definition of acute gout flare under development by the ACR

1.3 Protocol Amendment TMX-67_301.001 Summary of Changes

This document describes changes in reference to Protocol TMX-67_301.001, dated 20 January 2010. Please note that this amendment includes major changes to the overall study design and conduct of the study; therefore only an overview of the changes is provided in this section.

Change in Protocol	Rationale
Secondary Efficacy Endpoints Moved to Additional Endpoints	Since the majority of subjects will receive ULT that will decrease sUA <6.0 mg/dL, differences between treatment groups are no longer a relevant secondary endpoint
Removed ECGs from Safety Assessments	ECGs will be performed at the Visit and per the investigator's discretion should a cardiovascular event occur
Study Duration Changed to Approximately 5 Years and the Number of Subjects Increased to 7500	Complete event-driven trial in a shorter period of time
Change enrollment criteria to include subjects with (1) a serum urate level (sUA) ≥ 7 mg/dL or (2) with a sUA ≥ 6 mg/dL AND at least one flare in the 12 months prior to screening and/or the presence of tophi	Increase participation of gout subjects in safety study that may not have otherwise qualified due to sUA levels
Shortened washout period for prior urate lowering therapy to 7 days from 14 days	To make washout period consistent with duration appropriate for drug clearance and not to achieve hyperuricemic state
Introduce allopurinol titration (in 100 mg increments) based on sUA response to a maximum of 400 mg in subjects with moderate renal impairment and 600 mg in normal/mild renal impairment subjects (NOTE: Additional visits have been added at Weeks 6, 8 and 10 to monitor sUA response for those subjects who do not achieve sUA <6.0 mg/dL at the previous visit.)	Prevent subjects randomized to allopurinol from withdrawing from the study due to inadequate sUA response

Change in Protocol	Rationale
Investigator and sponsor will be unblinded to sUA levels until Week 12 visit (NOTE: both parties will remain blinded to study treatment.)	Assist in ensuring that subjects are titrated to a dose of study treatment that will maintain sUA <6.0 mg/dL for the 5 year study duration
Updated entry criteria for females to be ≥ 55 years of age and removed requirement for FSH testing	Women over age 55 are post-menopausal and confirmation via laboratory testing is not required
Updated protocol to remove any restrictions related to thiazide diuretic use	Any required allopurinol titration will occur in 100 mg increments and subjects will be monitored every 6 months during the course of the study
Revised Study Medication and Treatment Section due to inclusion of higher allopurinol doses and addition of placebo capsules	To maintain blinding, all subjects will be required to take 2 capsules of study medication daily
Updated schedule of events to reflect yearly physical exams	To follow typical clinical practice
Updated criteria for causality of adverse events	Align with company policy to utilize Yes or No response
Updated proposed CV event rate to 2.8%	Limited available information on true CV rate in high risk populations
Updated colchicine dosing recommendations for acute gout flares	Recently approved US labeling providing specific guidance regarding colchicine dosing
Deleted thyroid, and hs-crp	To streamline the study conduct; hematology and urinalysis will be done at screening and chemistry (including liver function tests) will be done at screening and at least every 6 months during the study
Added additional visits at Month 9 and Month 15 for elderly subjects and subjects with moderate renal impairment	To more frequently monitor LFTs and renal function in elderly subjects and subjects with moderate renal impairment
Removed the telephone contacts every 2 months after Month 12 visit for subjects still receiving study medication	Subjects will be seen in the clinic at least every 6 months; telephone contacts will still be made every 2 months for subjects who have discontinued study medication but are being followed for potential CV events.

Change in Protocol	Rationale
Clarified that detailed information on aspirin and NSAID use will be collected and specified how the analyses will account for use of these medications	Use of these medications could potentially confound the interpretation of study events
Specified details of signs and symptoms to be collected for gout flares	To apply the standardized definition of acute gout flare under development by the ACR

1.3 Protocol Amendment 3 Summary of Changes

This document describes changes in reference to Protocol TMX-67_301 Amendment 3, dated 26 January 2011.

Change in Protocol	Rationale
Update contacts for medical monitoring (medical advice on protocol, compound and medical management of subjects) and data management.	Takeda Global Research and Development, Inc. has contracted with vendors for medical monitoring and changed contracted vendor for data management responsibilities.
Update the approximate number of study sites from 450 sites to 465 sites.	Sites in Canada will be added to the study.
The follow up of subjects who discontinue prematurely from the study is clarified.	Subjects who prematurely discontinue study drug treatment and experience a CV event that is positively adjudicated as a MACE will no longer be followed.
Exclusion Criteria updated.	Criteria updated to eliminate possibility of subjects entering this study more than once.
Phone Follow-Ups clarified.	Clarification of expectations for collection of data at Phone Follow-ups.
Gout Flare and CV Event Sample Worksheets modified.	Text has been added to record investigator and subject information on all pages.
End of study Drug/End of Study Visits clarified.	Clarified the independence of the End of Study Drug and End of Study Visits eCRF.
Significant Protocol Deviations clarified.	Clarified that Significant Protocol Deviations should be captured in the eCRF.
Clarification on how the double-blinded nature of the study will be maintained added.	Clarification is response to FDA comment.
Additional Colchicine safety and drug interaction verbiage added.	Inform investigators of potential safety concerns and drug interactions in subjects who are given colchicine for prophylaxis.

1.3 Protocol Amendment TMX-67_301 Summary of Changes

This document describes changes in reference to Protocol TMX-67_301 Amendment 4, dated 19 May 2011.

Change in Protocol	Rationale
Remove the HIPAA regulation language throughout the protocol	HIPAA Privacy Rule provides federal protections for personal health information for the USA subjects only.

1.3 Protocol Amendment TMX-67_301.003 Summary of Changes

This document describes changes in reference to Protocol TMX-67_301 Amendment 4, dated 19 May 2011.

Change in Protocol	Rationale
Remove the HIPAA regulation language throughout the protocol	HIPAA Privacy Rule provides federal protections for personal health information for the USA subjects only.