Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, New Jersey 08816

KRYSTEXXA® (pegloticase)

Protocol No. M0401

Observational Study of the Use of KRYSTEXXA® (pegloticase) in Adult Hyperuricemic Patients with Gout Refractory to Conventional Therapy

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Sponsor: Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816
[redacted]

Sponsor Representative:

[redacted] _____ _____
signature date
Vice President, Clinical Affairs
and Interim Chief Medical Officer

Investigator signature page

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Investigator:

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. I agree to report all information or data in accordance with the protocol and, in particular, I agree to report all serious adverse experiences as defined in Section 3.8 of this protocol. I also agree to collect and handle all clinical specimens according to this protocol and supporting manuals.

_____	_____	_____
Principal/primary Investigator (type or print name)	signature	date

LIST OF EXTERNAL FACILITIES

Sponsor's representative for study conduct

[redacted]

929 North Front Street, Wilmington, NC 28401-3331

[redacted]

Bioanalytical laboratory facility

Millipore Corporation

15 Research Park Drive, Saint Charles, MO 63304

[redacted]

Central laboratory facility

LabConnect LLC

100 LabConnect Lane, Johnson City, TN 37615

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
C3	complement component 3
C4	complement component 4
CRF	case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
ELISA	enzyme-linked immunosorbant assay
FDA	Food and Drug Administration
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
IC	informed consent
ICH	International Conference on Harmonisation
i.v.	intravenous(ly)
IR	infusion reaction
IRB	Institutional Review Board
ITT	Intent to Treat
kDa	kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
NIAID/FANN	National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
NSAID	non-steroidal anti-inflammatory drug
PEG	polyethylene glycol
po	[per os] by mouth
PUA	plasma uric acid
SAE	serious adverse event
SAP	statistical analysis plan
Savient	Savient Pharmaceuticals, Inc.
SOP	standard operating procedure
SUA	serum uric acid
US	United States

PROTOCOL SYNOPSIS

Name of product	KRYSTEXXA® (pegloticase)
Drug substance:	Pegloticase is a uric acid-specific enzyme which is a polyethylene-glycol conjugated (PEGylated) product that consists of recombinant, modified, mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to monomethoxypoly(ethylene glycol) (mPEG; 10 kDa molecular weight). The cDNA coding for uricase is based on mammalian sequences. Each uricase subunit has a molecular weight of approximately 34 kilodaltons (kDa). The average molecular weight of pegloticase (tetrameric enzyme conjugated to a mean of 10.2 mPEG molecules) is approximately 540 kDa.
Protocol number:	M0401
Study title:	Observational study of the use of KRYSTEXXA® (pegloticase) in adult hyperuricemic patients with gout refractory to conventional therapy
Phase:	4
Objectives:	Primary: To evaluate the frequency and severity of infusion reactions (IRs), anaphylaxis, and immune complex-related events. Secondary: To identify serious adverse events (SAEs) associated with KRYSTEXXA therapy. To further evaluate the efficacy of KRYSTEXXA in this patient population of adult hyperuricemic patients with gout refractory to conventional therapy.
Study design:	This is a multicenter, open-label, single-arm observational study.
Investigational plan:	Approximately 1500 patients will be enrolled in order to observe treatment of up to 500 patients for a duration of 1 year. Patients who discontinue treatment before 51 weeks will be asked to remain in the study for follow-up assessments for the remainder of their planned treatment duration. The number of patients to be enrolled will be reassessed approximately 2 years after the first patient is enrolled. The study will be conducted at approximately 300 centers in the United States (US). It is estimated that approximately 2.5 years will be required for recruitment, from the first to the last patient's screening visit.

Treatment: Patients eligible for initial treatment with KRYSTEXXA 8 mg by intravenous (i.v.) infusion every 2 weeks will be offered enrollment into the observational study for a year. Serum uric acid (SUA) levels will be monitored prior to infusion and therapy will be discontinued if levels increase above 6 mg/dL on two consecutive measurements. If the SUA is noted to be above 6 mg/dl the sponsor suggests that a repeat SUA should be drawn when the result is noted to confirm, and if the 2 consecutive levels are noted to be above 6 mg/dL then it is advised to discontinue therapy.

Study duration: Approximately 63 weeks, including 51 weeks of treatment and 12 weeks of follow-up.

- Selection criteria

Inclusion criteria:

- Adult patients (age ≥ 18 years) with chronic gout refractory to conventional therapy, defined as patients who have failed to normalize SUA and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these drugs are contraindicated.
- Patients who have made the decision, along with their treating physician, to begin treatment with KRYSTEXXA.
- Patients who are willing and able to give informed consent and adhere to visit/protocol schedules (informed consent must be given before the first study procedure is performed).

Exclusion criteria:

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Non-compensated congestive heart failure
- Pregnancy or breast feeding
- Prior treatment with pegloticase or another recombinant uricase
- Known allergy to urate oxidase
- Prior treatment or concomitant therapy with a polyethylene glycol (PEG)-conjugated drug
- Recipient of an investigational drug within 4 weeks prior to study drug administration or plans to take an investigational agent during the study

Investigational drug: None

Reference therapy: KRYSTEXXA® (pegloticase) 8 mg i.v. every 2 weeks

Efficacy criteria: Normalization of SUA to < 6 mg/dL

Decrease in the number of swollen joints and the number of tender joints

Decrease in the frequency of gout flares

Reduction in the number of tophi

Safety criteria: IRs, anaphylaxis, and immune complex-related adverse events, serious adverse events and adverse event profile, including gout flares

Statistical methods: Descriptive statistics will be employed to summarize the proportion of responders, where a responder is defined as a patient whose SUA values were < 6 mg/dL at their final 2 consecutive study visits. Descriptive statistics will be provided for the number of swollen joints and tender joints at baseline, 6 months and 12 months or Early Discontinuation; for changes in numbers of gout flares based on patient reported history at 6-week intervals for Months 1-3 and 3-month intervals thereafter; and for change in the number of tophi at 6 months (Visit 13) and 12 months (Visit 26) or Early Discontinuation.

It is anticipated that there may be a considerable number of study patients who will drop out of the study. The sponsor will make every effort to identify the reason(s) for dropout before reaching the primary safety endpoint. For the analysis of each efficacy endpoint, various sensitivity analyses will be performed under different assumptions of potentially informative dropouts. For continuous efficacy variables, sensitivity analyses will be performed using standard mixed-effect model repeated measure (MMRM) methods. All the analyses will be summarized using 95% confidence interval estimates. The resulting summarized statistics for efficacy will be compared to those reported from the pre-approval phase 3 studies.

Adverse events will be summarized by presenting the proportion of patients having any adverse event (AE), overall and by body system, and by event as defined by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Separate summary tables will be provided for IRs, anaphylaxis AEs, and immune complex-related AEs.

For each type of the primary safety endpoints, one event, at most, will be counted per patient. The 95% (exact) confidence interval estimates for each type of safety endpoint will be reported for the rate of incidence both at the administrative interim analysis, for evaluating the feasibility of the study, and at the final analysis. The following hypothesis will be specifically tested: the rate of IRs seen in the phase 3 studies will be reduced in this study by monitoring SUA prior to infusions and

discontinuing therapy in patients if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. With at least 500 patients enrolled with 1 year follow-up, the power of detecting a 26% IR rate (the observed value from the pre-approval phase 3 studies) against 13% is at least 90%. The rate of IRs reported during the study will be reported and compared descriptively to the rates observed in the pre-approval phase 3 studies.

There is no planned interim analysis. However, the number of enrolled patients will be reassessed approximately 2 years after the first patient is enrolled. This data will be utilized to make a prediction concerning the future enrollment profile. The enrollment goal may be adjusted depending on the drop-out rate such that approximately 500 patients will complete the 1 year treatment period.

Assessments:

Baseline samples for identification of antibodies to pegloticase and to PEG, and determination of complement markers (complement component 3 [C3] and complement component 4 [C4]) and tryptase levels. Antibody samples at End-of-Study and at 3-month intervals during follow-up after discontinuation of treatment.

Review of concurrent medications, co-morbidities, and compliance with premedication regimes for gout flares.

Determination of SUA before each infusion.

Recording of drug, dose and timing of IR prophylactic medications.

Recording of infusion start and finish times, sodium chloride diluent used and the total volume infused.

Swollen joint and tender joint counts, and number of tophi to be assessed at baseline, 6 months (Visit 13) and 12 months (Visit 26) or Early Discontinuation.

Flares:

- At baseline, document the history of gout flares from the previous 6 months
- Documentation of the occurrence and duration of any gout flares experienced while the patient is participating in the study

IRs and anaphylaxis:

- Documentation of signs and symptoms and onset time in relation to the initiation of the KRYSTEXXA infusion, and treatment, if any
- Follow-up laboratory assessments may include the collection of samples for analysis of antibodies to pegloticase and PEG, anti-pegloticase IgE, C3, C4, and tryptase levels.

Immune complex disease:

- Clinical investigation of a presumptive immune complex disease (as per clinical practice) and of complement markers (C3, C4) will be pursued.

CONTACT INFORMATION

Reporting of serious adverse events (SAEs) to sponsor or sponsor's representative

ANY SERIOUS ADVERSE EVENT, OR DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY PATIENT ENTERED INTO THE STUDY, WHETHER OR NOT RELATED TO KRYSTEXXA, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUALS LISTED BELOW. ALL PATIENTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED FOR OUTCOME.

Primary contact information

[redacted]
5150 McCrimmon Parkway
Morrisville, NC 27560
[redacted]

Corporate sponsor's contact information

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard (14th Floor)
East Brunswick, NJ 08816
[redacted]

[redacted]
Director, Clinical Development
[redacted]

If none of the above can be reached:

Savient Pharmaceuticals, Inc. at [redacted]

1 INTRODUCTION

1.1 Disease Background

Gout is a disease resulting from the body's inflammatory response to urate crystals that deposit in tissues and joint spaces in susceptible individuals with chronic hyperuricemia (Dalbeth and Haskard, 2005). Uric acid, the end metabolite of purine metabolism in humans, is poorly soluble in serum at concentrations above 6.8 mg/dL. Most mammals, with the exception of humans, have an endogenous intracellular hepatic uricase that converts uric acid into allantoin, a highly soluble and easily excreted end metabolite (Wu et al, 1992). Uric acid production and excretion are normally balanced in the human body, maintaining a serum concentration below the limit of urate solubility. However, this balance may be disturbed by decreased excretion, overproduction, or a combination of these factors leading to hyperuricemia (Kanellis et al, 2006). Hyperuricemia itself is not associated with symptoms or signs of disease but in the context of gout, prolonged hyperuricemia leads to precipitation of monosodium urate crystals in and around joints and other tissues and the evolution of defining clinical manifestations. The hallmark symptoms of gout are related to acute inflammatory monoarticular arthritis, lasting days or weeks and causing exquisite pain, i.e., an acute gout flare. Protracted hyperuricemia may lead not only to frequent gout flares, but may result in urate nephropathy and renal calculi, and gout tophi (nodular deposits of urate crystals and inflammatory cells) in joints, soft tissues, bones, and in some organs. The cornerstone of gout therapy is treatment of hyperuricemia with urate-lowering drugs (Becker and Jolly, 2005).

Refractory gout occurs in a subset of symptomatic gout patients whose hyperuricemia cannot be controlled with conventional xanthine oxidase inhibitors at the maxiumum medically appropriate dose. The hyperuricemia of most gout patients can be controlled successfully with a xanthine oxidase inhibitor (e.g., allopurinol) to reduce uric acid formation or agents such as probenecid that promote uric acid excretion (uricosuric drugs). Although failure of patient compliance in the daily use of allopurinol or uricosuric drugs is often the root cause of treatment failure (Stamp et al, 2000), allopurinol therapy at a maximum medically appropriate dose is sometimes ineffective in normalizing the serum uric acid (SUA), or may be contraindicated in patients with impaired renal function or in patients with allopurinol hypersensitivity (Hande et al, 1984; Singer and Wallace, 1986; and Arellano and Sacristan, 1993). Uncontrolled or inadequately controlled hyperuricemia leads to increasing frequency and severity of gout-related symptoms and chronic disease, e.g., gout flares, tophi, gouty arthritis, and urate nephropathy. Chronic gout may lead to joint destruction and disability. For these individuals, no effective therapies have been available to normalize the circulating uric acid as a means of slowing or reversing the progress of the disease.

1.2 KRYSTEXXA Background

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. KRYSTEXXA is a uric acid-specific enzyme which is a

polyethylene glycol -conjugated (PEGylated) product that consists of recombinant, modified, mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to monomethoxypoly(ethylene glycol) (mPEG; 10 kDa molecular weight). KRYSTEXXA achieves its therapeutic affect by catalyzing the oxidation of uric acid to the much more soluble allantoin, thereby lowering SUA with allantoin readily eliminated, primarily by renal excretion.

Additional background concerning KRYSTEXXA can be found in the current version of the Food and Drug Administration (FDA)-approved KRYSTEXXA Full Prescribing Information.

1.2.1 Efficacy Assessments in Clinical Studies of KRYSTEXXA

The safety and efficacy of KRYSTEXXA® (pegloticase) has been evaluated in 7 clinical studies, including 2 replicate, multicenter, randomized double-blind, placebo-controlled studies of 6-month duration. In the two placebo-controlled studies, adult patients with chronic gout refractory to conventional therapy were randomized to receive intravenous (i.v.) infusions of KRYSTEXXA 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. All patients also received prophylaxis for infusion reactions (IRs) and for gout flares. To assess the efficacy of KRYSTEXXA in lowering uric acid, the primary endpoint in both trials was the proportion of patients who achieved plasma uric acid (PUA) less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. A greater proportion of patients treated with KRYSTEXXA every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo (38% to 47% of patients receiving KRYSTEXXA vs. 0% of patients receiving placebo). In addition, at Month 6, the percentage of patients who achieved a complete resolution of tophi (defined as 100% resolution of at least 1 target tophus, the appearance of no new tophi, and no single tophus showed progression) was 45%, 26% and 8% with KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Although the 4 week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with an increased frequency of IRs and was less efficacious with respect to tophi. Therefore, pegloticase 8 mg every 2 weeks was approved by the US FDA on September 14, 2010 for the treatment of adult patients with chronic gout refractory to conventional therapy.

1.2.2 Safety Assessments in Clinical Studies of KRYSTEXXA

The most commonly reported serious adverse reactions from the pre-marketing controlled clinical trials in patients treated with KRYSTEXXA 8 mg every 2 weeks were gout flare, IR, and anaphylaxis.

Gout flares were more frequent during the first 3 months of treatment (74% in KRYSTEXXA-treated patients vs. 51% in placebo-treated patients), and seemed to decrease over the next 3 months (41% KRYSTEXXA vs. 67% placebo). An increase in gout flares is frequently observed upon initiation of anti-hyperuremic therapy. Thus, all patients in these studies received non-steroidal anti-inflammatory drugs (NSAID) or colchicine or both for at least 7 days as gout flare prophylaxis before beginning KRYSTEXXA; patients continued on this regimen for the 6-month treatment duration.

All patients in Phase 3 clinical trials were pre-treated with an oral antihistamine (fexofenadine, 60 mg by mouth [po], the night before and morning of the infusion), i.v. corticosteroid (200 mg hydrocortisone i.v.) and acetaminophen (1000 mg po) before the infusion to prevent anaphylaxis and IRs. Nevertheless, IRs were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks compared to 5% of patients treated with placebo. Manifestations of IRs included urticaria, dyspnea, chest discomfort, chest pain, erythema, and pruritus. Approximately 3% of IRs occurred with the first dose, and most (91%) occurred during the infusion rather than after it was completed.

None of the IRs which occurred in the pegloticase studies was categorized as anaphylaxis by the investigators who enrolled subjects in the Phase 2, Phase 3, or open-label extension studies. The US FDA performed a retrospective analysis of the IRs to assess for anaphylaxis, using modified National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria (Sampson et al, 2006). Using their analysis, the frequency of anaphylaxis was 6.5% in all patients treated with KRYSTEXXA 8 mg every 2 week. During randomized, placebo-controlled studies, the frequency was 5% compared to none with placebo. An independent immunologist commissioned by the sponsor to review the data based strictly upon the NIAID/FAAN clinical criteria for anaphylaxis determined the overall rate in the clinical studies to be 2.4%.

A retrospective analysis of the data from the Phase 3 trials revealed that most IRs occurred when uric acid values were above 6 mg/dL. Importantly, other than one case that met the criteria for anaphylaxis occurring during the first dose of pegloticase (8 mg), all other cases that met the criteria for anaphylaxis occurred when a subject's last uric acid value was above 6 mg/dL. Thus, the monitoring rule was developed and incorporated into the FDA-approved Full Prescribing Information:

"Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed."

Other non-serious AEs reported in ≥ 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks included nausea (12%), contusion or ecchymosis (11%), nasopharyngitis (7%), constipation (6%), chest pain (6%) and vomiting (5%).

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titers (> 1:2430) were associated with both a failure to maintain pegloticase-induced normalization of uric acid and a higher incidence of IRs. Because of this high rate of antibody development, one of the specific safety endpoints in the larger population for the current study will be to determine if there is a risk of immune complex disease in patients treated with KRYSTEXXA. No cases of immune complex disease were identified in the pre-marketing controlled clinical studies.

While KRYSTEXXA has not been formally studied in patients with congestive heart failure, there were some patients who experienced exacerbation during the clinical studies. It was

therefore recommended that treating physicians exercise caution when using KRYSTEXXA in patients who have congestive heart failure and to monitor patients closely following infusion.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a contraindication for KRYSTEXXA due to the risk of hemolysis and methemoglobinemia in these patients. Therefore, all patients in this study must be screened for this enzyme deficiency.

Refer to the current version of the FDA-approved KRYSTEXXA Full Prescribing Information and Pegloticase Investigators Brochure for detailed information concerning the safety profile of KRYSTEXXA.

1.3 Study Rationale

This Phase 4, observational study is primarily focused on evaluating the frequency and severity of IRs, anaphylaxis, and immune complex-related AEs in adult patients with chronic gout refractory to conventional therapy who are being treated with KRYSTEXXA. In the post-approval setting, this study also provides a means of identifying and assessing any SAEs associated with KRYSTEXXA therapy. The efficacy of KRYSTEXXA, in terms of normalizing SUA and decreasing the number of swollen joints and tender joints, reducing gout flares, and resolving tophi in this patient population can also be further evaluated in a large population within the standard healthcare setting.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of the study is to evaluate the frequency and severity of IRs, anaphylaxis, and immune complex-related events.

2.2 Secondary

Secondary objectives are to identify SAEs associated with KRYSTEXXA therapy and to further evaluate the efficacy of KRYSTEXXA in this patient population of adult hyperuricemic patients with gout refractory to conventional therapy.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

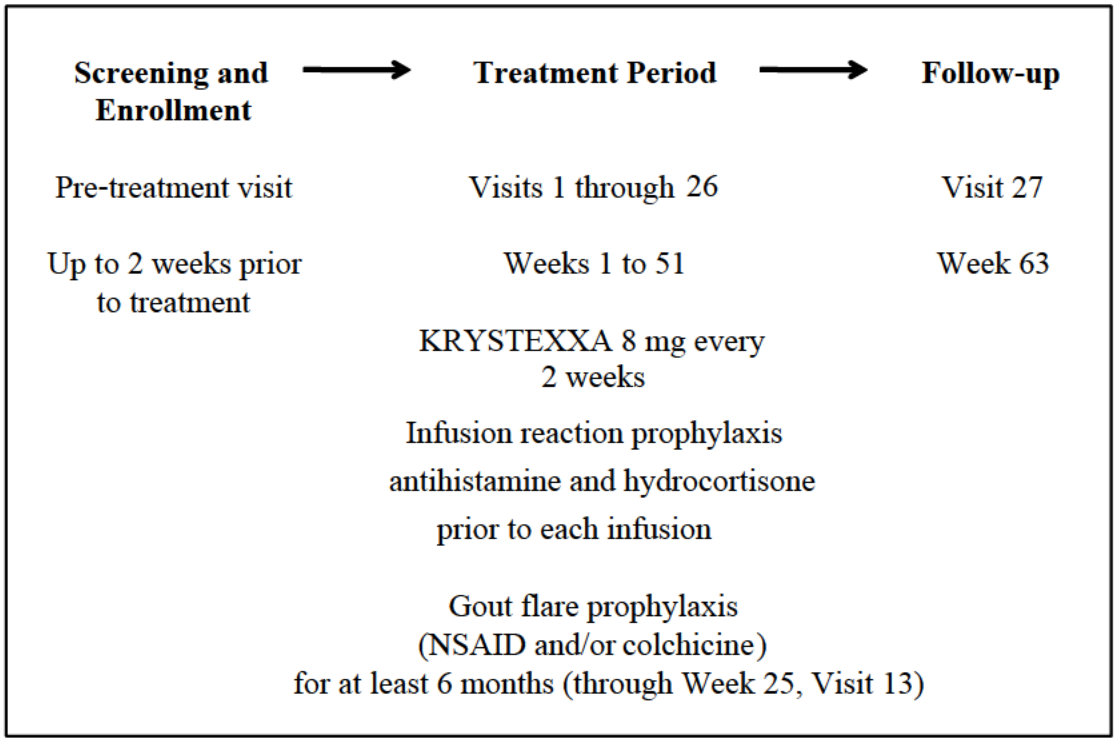
This is a Phase 4, multicenter, open-label, single-arm observational study of KRYSTEXXA 8 mg i.v. every 2 weeks in adult hyperuricemic patients with gout refractory to conventional therapy. Approximately 1500 patients will be enrolled in order to observe treatment of up to 500 patients at approximately 300 centers in the United States (US). Study duration is approximately 63 weeks, including 51 weeks of treatment and 12 weeks of follow-up. Patients who discontinue treatment before 51 weeks (i.e., before all 26 planned KRYSTEXXA infusions) will be asked to remain in the study for follow-up assessments for the remainder of their planned treatment duration. It is estimated that approximately 2.5 years will be required for recruitment, from the

first to the last patient's screening visit. The number of patients to be enrolled will be reassessed approximately 2 years after the first patient is enrolled.

Patients not already on a prophylactic regimen of colchicine or NSAID to prevent gout flares should be placed on one of these agents at the time of study entry, unless medically contraindicated (see Section 3.5.7.1). All patients will receive KRYSTEXXA 8 mg i.v. every 2 weeks, admixed in 250 mL of 0.45% or 0.9% Sodium Chloride Injection, USP for i.v. infusion over a target infusion time of 120 minutes. Standardized infusion reaction prophylaxis consisting of pre-treatment with antihistamines and corticosteroids will accompany each infusion (see Section 3.5.8.1). The drug name, dose and timing of these prophylactic medications will be recorded.

A schematic diagram of the study design appears in Figure 1, and the Schedule of Procedures and Evaluations is located in Appendix 3.

Figure 1 Study Design



3.2 Discussion of Design

The primary objective of this Phase 4, observational study is to further evaluate the frequency and severity of IRs, anaphylaxis, and immune complex-related events in patients receiving treatment with KRYSTEXXA. Anaphylaxis and IRs were frequently reported (> 5% of subjects) AEs in the pivotal Phase 3 studies involving KRYSTEXXA, and immune complex-related AEs are a concern with any biological agents (Chen, 2010). For this study, the following will apply:

- IRs will be defined as any AE or cluster of AEs, not attributable to another cause, that occurs during or within 2 hours after the infusion of KRYSTEXXA. Other cases that occur outside of the 2-hour window may also be categorized as an IR as per investigator discretion.
- Anaphylaxis will be defined using the NIAID/FANN criteria (Sampson et al, 2006), comprised of involvement of the skin or mucosal tissue and either respiratory compromise or reduced blood pressure or associated symptoms of end-organ dysfunction (refer to Table 1). Mast cell involvement in any constellation of signs and symptoms will be evaluated by measuring serum tryptase levels.
- Immune complex-related AEs will be defined as any presumptive immune complex-related disorders that are confirmed by an appropriate investigation of the disease and of complement markers (complement component 3 [C3], complement component 4 [C4]). Clinical manifestations could include skin rash, arthralgia, arthritis, and proteinuria (see Section 3.8.1.3).

The proposed patient number (approximately 1500 enrolled patients in order to observe treatment of up to 500 patients for a duration of 1 year) and 1-year duration of the study will significantly extend the patient exposure to KRYSTEXXA compared with the pre-marketing controlled clinical trials.

In addition, post-hoc analyses of the clinical study data demonstrated that if KRYSTEXXA had been stopped when a patient's uric acid level rose to greater than 6 mg/dL at 2 consecutive visits, the incidence of IRs would have been reduced by half and there would have been little change in the efficacy outcome. Current guidance for the use of KRYSTEXXA thus recommends monitoring SUA levels prior to infusions and considering discontinuing treatment if SUA levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. This study will follow this guidance and provides for the collection of data on both SUA levels and IRs to extend the knowledge base regarding the relationship between these factors.

The design of this study follows the FDA-approved Full Prescribing Information for the use of KRYSTEXXA and allows for capturing additional data related to the safety and efficacy of KRYSTEXXA within the standard healthcare setting. Efforts have been made to limit study-specific activities for the enrolled patients and participating healthcare providers while still allowing for a robust assessment of key safety and efficacy features of KRYSTEXXA treatment in this patient population.

3.3 Study Population

3.3.1 Patient Population

The patient population in this study will be hyperuricemic (SUA > 6 mg/dL) adult men and women (age ≥ 18) diagnosed with chronic gout and who are refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize SUA and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the

maximum medically appropriate dose or for whom these drugs are contraindicated. To enter this study, the patient and the physician must have decided to begin treatment with KRYSTEXXA.

The sample size for the study will be approximately 500 patients treated for one year. This sample size is a pragmatic one that will allow enough patients to enroll in a suitable time period for evaluation of the frequency and severity of IRs, anaphylaxis and immune complex-related AEs and to identify SAEs associated with KRYSTEXXA therapy in this post-approval, observational study.

3.3.2 Inclusion and Exclusion Criteria

3.3.2.1 Inclusion Criteria

Patients are eligible for the study if all of the following apply:

- Adult patients (age ≥ 18 years) with chronic gout refractory to conventional therapy, defined as patients who have failed to normalize SUA and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these drugs are contraindicated.
- Patients who have made the decision, along with their treating physician, to begin treatment with KRYSTEXXA.
- Patients who are willing and able to give informed consent and adhere to visit/protocol schedules (informed consent must be given before the first study procedure is performed).

3.3.2.2 Exclusion Criteria

Patients will be excluded from participation in the study if any of the following apply:

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Non-compensated congestive heart failure
- Pregnancy or breast feeding
- Prior treatment with pegloticase or another recombinant uricase
- Known allergy to urate oxidase
- Prior treatment or concomitant therapy with a polyethylene glycol (PEG)-conjugated drug
- Recipient of an investigational drug within 4 weeks prior to study drug administration or plans to take an investigational agent during the study

3.4 Treatments

3.4.1 Investigational Drug and Reference Therapy

3.4.1.1 Investigational Drug

No investigational drug will be utilized in this post-market, observational study.

3.4.1.2 Reference therapy

KRYSTEXXA is commercially available in the US as a sterile, clear, colorless solution containing 8 mg/mL pegloticase in phosphate-buffered saline. KRYSTEXXA® (pegloticase) concentrations are expressed as concentrations of uricase protein. Each mL of KRYSTEXXA contains 8 mg of uricase protein conjugated to 24 mg of 10 kDa monomethoxypoly(ethylene glycol) (mPEG). Excipients include disodium hydrogen phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dihydrate and water for injection.

KRYSTEXXA is supplied in a single-use, 2 mL glass vial with a Teflon coated (latex-free) rubber injection stopper to deliver KRYSTEXXA as 8 mg of uricase protein in 1 mL volume for i.v. infusion. Before preparation for use, KRYSTEXXA should be stored in the carton, maintained under refrigeration between 2ºC and 8ºC (36ºF and 46ºF), protected from light and should not be shaken or frozen.

3.4.2 Treatment Assignment

All patients will receive KRYSTEXXA 8 mg by i.v. infusion every 2 weeks.

3.4.3 Blinding

This is an open-label study.

3.4.4 Treatment Compliance

All doses of KRYSTEXXA will be administered in a healthcare setting by healthcare professionals. The number of doses and amount of each dose received by each patient will be captured in the patient's medical record and in the case report form (CRF)/electronic case report form (eCRF).

3.4.5 Concomitant Therapy

Pharmaceutical agents specifically indicated for lowering SUA (e.g., allopurinol) should not be used in conjunction with KRYSTEXXA. KRYSTEXXA is indicated for use in patients with chronic gout whose signs and symptoms are inadequately controlled with conventional therapy (i.e., xanthine oxidase inhibitors such as allopurinol). If a patient is being followed after discontinuation of KRYSTEXXA (see Section 3.5.3), another urate-lowering drug may be instituted at any time.

All medications taken for concurrent medical conditions and any required analgesics must be recorded in patients' medical records and in the CRF/eCRF. Data captured on the use of concomitant medications will include the name of the drug, and if known, the start date, stop date and indication.

The use of all other investigational drugs is prohibited throughout the study.

3.5 Visit Schedules and Assessments

The schedule of visits and assessments can be found in Appendix 3.

3.5.1 Screening Procedures

Prior to entry into the protocol, the nature and risks of the study must be reviewed with each patient. Each patient or each patient's legal representative must be given the opportunity to read the Institutional Review Board's (IRB) approved informed consent (IC) form and ask questions. After all questions raised by a potential participant are answered, and before any protocol-specified screening procedures are initiated, each patient or each patient's legal representative must sign and date the consent form. A copy of the signed and dated IC form must be provided to the patient.

After IC is obtained, a 6-digit patient number will be assigned. The first three digits of each patient number will represent the site and the last three will be unique for each patient at each site. Potential patients will be screened to determine if they satisfy all inclusion and exclusion criteria. All screening procedures must be completed prior to dosing. Specified CRF/eCRF pages to report basic demographic information and reason(s) for exclusion must be completed for all patients who signed an informed consent form, but never received KRYSTEXXA.

The following evaluations will be performed on each patient and results recorded in the medical record and CRF/eCRF:

- Informed consent (process must be documented in the medical record)
- Medical history – include all clinically significant medical problems within the past 5 years, but excluding gout history which will be separately documented
- Gout history and symptom severity
    - Documentation of the contraindication to or the failure of conventional therapy at the maximum medically appropriate dose
    - Number of gout flares in the last 6 months, and most recent occurrence
    - Assessment of tophi and gouty arthritis, including a count of the total number of palpable subcutaneous and subperiosteal tophi, if accessible
    - The number of tender joints and swollen joints
    - Documentation of the history of gout-related kidney disease
- Physical examination (including but not limited to dermatological, head and neck, chest and cardiac, abdominal, musculoskeletal, and nervous system examination)
- Vital signs and height and body weight
- Obtain a blood sample for analysis of SUA
- Obtain a blood sample for G6PD testing

- Review concomitant medications
- Initiate gout flare prophylaxis and advise patient to contact site within 12 hours of gout flare symptom onset. If prophylaxis is contraindicated, document the reason.
- Advise patient of the IR prophylaxis regimen to be used before each scheduled KRYSTEXXA infusion.

3.5.2 Study Procedures

3.5.2.1 Visits 1 through 26

At each visit, the following procedures must be completed **before administration of KRYSTEXXA**:

- Provide the KRYSTEXXA Medication Guide and answer any questions the patient has.
- Review concomitant medications, and question patient about any new medical conditions.
- Record all new clinically significant medical conditions in both the medical record and on the adverse event CRF/eCRF and evaluate for the occurrence of an acute gout flare since the previous visit.
- After the first visit, serum uric acid (SUA) levels will be monitored prior to the next infusion and therapy will be discontinued if levels increase above 6 mg/dL on two consecutive measurements. If the SUA is noted to be above 6 mg/dl the sponsor suggests that a repeat SUA should be drawn when the result is noted to confirm, and if the 2 consecutive levels are noted to be above 6 mg/dL then it is advised to discontinue therapy.
- Record blood pressure, heart rate, respiratory rate and temperature shortly before study drug infusion.
- If patient has not had SUA analyzed between his/her last visit and the current one, obtain blood samples for analysis of SUA.
- Record self-administered pre-medications the patient took for prophylaxis against infusion reactions, and administer hydrocortisone (see Section 3.5.8). Record the drug name, dose, route and time of administration of each medication.

At Visit 1, but not routinely for other visits, also obtain blood samples for baseline determination of complement components (C3, C4), tryptase level, and identification of antibodies to pegloticase or PEG. These baseline samples will be stored for later analysis to compare with blood samples that are collected at subsequent visits to assess these parameters as part of the evaluation of an IR or potential immune-complex related event (see Section 3.5.8.3).

Following completion of the above procedures:

- Administer KRYSTEXXA (admixed in 250 mL 0.45% or 0.9% Sodium Chloride Injection, USP) by i.v. infusion over 120 minutes. Record the infusion start and finish times, and total volume infused. Details regarding study drug preparation and administration can be found in Section 7.2 and are described in the FDA-approved KRYSTEXXA Full Prescribing Information.
- Follow standard procedures at the center at which the infusion is being performed to monitor for IRs.
- Monitor for AEs during the infusion. See Section 3.5.8 for management and documentation of possible infusion-related reactions.
- Patients may be discharged after an appropriate period of time for post-infusion observation (approximately 1 hour after completion of the infusion is recommended).
- Monitor therapy by providing the patient with a laboratory slip and advising him/her to have blood drawn for analysis of SUA prior to the next dosing visit.

3.5.2.2 Visits 13 and 26

In addition to the study procedures listed for Visits 1 through 26, the following assessments will also be collected at 6 months (Visit 13) and 12 months (Visit 26) after initiating treatment with KRYSTEXXA:

- Perform swollen joint and tender joint counts
- Perform a count of the total number of palpable subcutaneous and subperiosteal tophi, if accessible

3.5.2.3 Visit 27: End of Study

The final procedures at End of Study (Visit 27) (12 weeks after final KRYSTEXXA infusion) will include:

- Inquire and assess for AEs, gout flares and changes in concomitant medications since previous study visit
- Complete physical exam, reviewing same body systems as at screening visit
- Measure blood pressure, heart rate and temperature
- Collect blood samples for identification of antibodies to pegloticase or PEG
- Record SUA results obtained after the last infusion
- Instruct patients on post-study anti-hyperuricemic therapy as appropriate

3.5.3 Early Treatment Discontinuation Procedures

Patients in whom KRYSTEXXA is discontinued before Visit 26 will be asked to continue in follow-up for the full duration of the study. In this case, patients are to return 4 weeks (+/- 5

days) after their final infusion of KRYSTEXXA in order to undergo early treatment discontinuation study procedures. Patients who discontinue treatment before 51 weeks (i.e., before all 26 planned KRYSTEXXA infusions) will be asked to remain in the study for follow-up assessments for the remainder of their planned treatment duration. These procedures include essentially the same procedures as Visit 26, adding only the final instruction to patients:

- Inquire and assess for AEs, gout flares and changes in concomitant medications since previous study visit
- Determine and record the reason for the early discontinuation of KRYSTEXXA
- Complete physical exam, reviewing same body systems as at screening visit
- Measure blood pressure, heart rate and temperature
- Collect blood samples for antibodies to pegloticase or PEG
- Perform swollen joint and tender joint count
- Perform a count of the total number of palpable subcutaneous and subperiosteal tophi, if accessible
- Instruct patients on post-KRYSTEXXA anti-hyperuricemic therapy as appropriate

Additional Follow-up Visit Procedures

The first follow-up visit will be 3 months (12 weeks) after the last KRYSTEXXA infusion, and at 3-month intervals subsequently. Follow-up visits will only be conducted for the remainder of the patient's planned 1 year of study participation. For example, subjects who discontinue treatment on or after Visit 19 would only have an Early Treatment Discontinuation Visit (at 4 weeks after discontinuation) and a 3-month post-treatment follow-up visit.)

Assessments during the post-treatment follow-up period will include:

- Inquire and assess for AEs, gout flares and changes in concurrent medications since previous study visit
- Collect blood samples for identification of antibodies to pegloticase or PEG

3.5.4 Early Discontinuation from the Study

Patients who completely discontinue their participation in the study and do not consent to be followed for the full year are to return 4 weeks (+/- 5 days) after their final infusion of KRYSTEXXA in order to undergo early discontinuation study procedures. These procedures include essentially the same procedures as Visit 26, but without SUA and adding only blood samples for antibodies and the final instruction to patients:

- Inquire and assess for AEs, gout flares and changes in concomitant medications since previous study visit
- Determine and record the reason for the early discontinuation of the patient

- Complete physical exam, reviewing same body systems as at screening visit
- Measure blood pressure, heart rate and temperature
- Collect blood samples for antibodies to pegloticase or PEG
- Perform swollen joint and tender joint count
- Perform a count of the total number of palpable subcutaneous and subperiosteal tophi, if accessible
- Instruct patients on post-study anti-hyperuricemic therapy as appropriate

3.5.5 Interruption of Treatment

Dosing with KRYSTEXXA may be delayed or interrupted for example, for vacation or for intercurrent illness, without requiring a patient to be discontinued from the study. The reason for the delay or interruption will be captured in both the medical record and the CRF/eCRF. If the SUA is >6 mg/dL after an interruption in treatment, the patient may still resume treatment.

3.5.6 Patient Discontinuation from Study

Patients may be discontinued from the study if they withdraw consent, if they experience an AE that precludes further participation, if they are non-compliant with study procedures, if there is a protocol violation, or if treatment is discontinued due to elevation of SUA >6 mg/dL. The reason for a patient not completing the study will be collected and recorded in the patient's medical record and on the CRF/eCRF. If a patient is discontinued from the study, every effort should be made to complete the procedures for an early discontinuation (see Section 3.5.4), preferably 4 weeks after their last dose of KRYSTEXXA but sooner if necessary. AEs that are possibly or probably drug-related, are of moderate or greater severity and are ongoing when a patient is discontinued or at the final visit will be followed up to 30 days, or until the event resolves or stabilizes, whichever is sooner. Follow-up may entail only a phone call, or it may require additional examinations or laboratory evaluations, depending upon the event. Documentation of the follow-up will be included in the patient's medical record and a summary will be provided to Savient or designee for possible inclusion in the clinical study report.

Patients who discontinue KRYSTEXXA, for example due to an IR or an elevation of SUA >6 mg/dL, will be asked to remain in the study in follow-up for the remainder of their planned treatment duration (see Section 3.5.3). In this case, the reason for KRYSTEXXA discontinuation will be collected and recorded in the patient's medical record and on the CRF/eCRF. The medical monitor must be notified as soon as possible about any patient's discontinuation.

3.5.7 Gout flare Prophylaxis and Treatment

3.5.7.1 Gout flare Prophylaxis

All patients should receive prophylactic treatment to reduce the risk of acute gout flares, unless medically contraindicated or not tolerated as noted in the FDA-approved KRYSTEXXA Full

Prescribing Information. The patient should begin a regime of colchicine or NSAID prophylaxis at least 1 week before the first dose of KRYSTEXXA and it should continue for at least 6 months after initiation of KRYSTEXXA therapy.

3.5.7.2 Gout flare Treatment

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. **Patients are to be instructed to contact the site within 12 hours from the onset of symptoms. Gout flares should be confirmed through questioning or direct observation.** It is recommended that all patients who experience a gout flare during the study should receive an anti-inflammatory treatment (e.g., NSAIDS, colchicine, corticosteroids) as clinically deemed indicated by the treating physician.

3.5.8 Infusion Reactions

An IR will be defined as any AE or cluster of AEs, not attributable to another cause, that occurs during or within 2 hours after the infusion of KRYSTEXXA. Other cases that occur outside of the 2-hour window may also be categorized as an IR as per investigator discretion. Signs and symptoms of the event, and treatments administered, must be documented in the medical record and in the CRF/eCRF. Examples of events not considered as possible IRs include laboratory abnormalities that are unlikely to have occurred during or within 2 hours following the infusion (e.g., anemia, hypercholesterolemia), gout flares, most infectious diseases, or the recurrence or worsening of a known chronic medical problem identified in the patient's medical history.

3.5.8.1 Infusion Reaction Prophylaxis

Infusion reactions are not uncommon when biological agents are administered by i.v. infusion. Therefore, all patients will receive pre-treatment prophylaxis consisting of at least an antihistamine and corticosteroid prior to each infusion of KRYSTEXXA. In order to standardize this regimen, patients will use 60 mg fexofenadine po the night before and the morning of the infusion and 200 mg hydrocortisone iv before the infusion. If the investigator feels this regimen is not appropriate for an individual patient, s/he should contact the medical monitor to discuss alternative therapy. The name, dose and time of administration of each prophylactic medication will be recorded in the medical record and in the CRF/eCRF.

3.5.8.2 Anaphylaxis

For this study, anaphylaxis, an allergic reaction that is rapid in onset, can be serious, and may cause death, will be defined using the NIAID/FANN diagnostic clinical criteria (Sampson et al, 2006) as described in Table 1 below. This constellation of signs and symptoms will be documented in the medical record and in the designated CRF/eCRF page. All IRs, whether described as anaphylaxis or not, will be adjudicated for anaphylaxis based on the criteria below (refer to Section 3.9).

Table 1 NIAID/FANN Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when the following criteria are fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; swollen lips, tongue, or uvula)
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b. Reduced blood pressure (i.e., systolic blood pressure < 90 mm Hg or greater than 30% decrease from that person's baseline) or associated symptoms of end-organ failure (e.g., hypotonia [collapse], syncope, incontinence)

NIAID/FANN: National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network

3.5.8.3 Management of Infusion-related Adverse Events

Refer to the Full Prescribing Information for general management of infusion-related adverse events. In addition, for this study, if a patient experiences an IR, the following procedures will be undertaken:

- an abbreviated physical examination to capture medically relevant details, including but not limited to a thorough dermatologic examination looking for erythema, hives or peri-oral or lingual edema; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heart beat.
- vital signs (temperature, respiratory rate, heart rate, blood pressure) will be captured at least every 30 minutes until the resolution or stabilization of the event.
- a 12-lead ECG with rhythm strip will be obtained and analyzed for any serious IR or any IR with angina chest discomfort, chest tightness, shortness of breath, or other cardiac symptoms.
- blood samples will be obtained for measurement of tryptase (as a marker for mast cell degranulation), C3, C4, and identification of antibodies to pegloticase (IgM, IgG, IgE) or to PEG.

The Investigator may administer any medically indicated pharmacologic agent intended to relieve symptoms (caution: no other drugs can be mixed in the KRYSTEXXA infusion bag). Signs and symptoms of the event and drugs given for treatment are to be recorded in the medical record and in the CRF/eCRF.

If in the Investigator's opinion the patient is experiencing an anaphylactic reaction (symptoms of stridor, wheezing, or cardiovascular instability, especially if associated with generalized

urticaria, pruritus, flushing, or mucosal edema), treatment with KRYSTEXXA should be permanently discontinued.

3.6 Efficacy Assessments

3.6.1 Serum Uric Acid Levels

The efficacy endpoint in this study is normalization of SUA to < 6 mg/dL. Serum uric acid will be measured using a standard clinical assay performed at local laboratories. Blood will be collected several days prior to each KRYSTEXXA infusion for the determination of SUA levels (see Section 3.5.2).

3.6.2 Clinical Outcomes

3.6.2.1 Number of Swollen Joints and Tender Joints

A count of the number of swollen joints and tender joints will be performed at Baseline/Screening, at 6 months (Visit 13) and at 12 months (Visit 26) or Early Discontinuation.

3.6.2.2 Gout flares

The occurrence and duration of gout flares will be reported throughout the study. The number of gout flares will be assessed by 6-week intervals for the first 3 months, and by 3-month intervals through the end-of-study.

3.6.2.3 Number of Tophi

A count of the total number of palpable subcutaneous tophi will be performed at Baseline/Screening, at 6 months (Visit 13) and at 12 months (Visit 26) or Early Discontinuation.

3.7 Safety Assessments

3.7.1 Adverse Event Profile

Safety assessments will be focused on a further evaluation of the AE profile of KRYSTEXXA. All AEs and SAEs will be monitored and recorded. Special emphasis will be placed on capturing details of events that occur during the infusion or within 1 hour after the infusion of KRYSTEXXA in order to facilitate the characterization of infusion-related reactions, including anaphylaxis. As KRYSTEXXA is a biological agent, the development of immune complex-related AEs will also be carefully scrutinized.

- IRs will be defined as any AE or cluster of AEs, not attributable to another cause, that occurs during or within 2 hours after the infusion of KRYSTEXXA. Other cases that occur outside of the 2-hour window may also be categorized as an IR as per investigator discretion.
- Anaphylaxis will be defined using the NIAID/FANN criteria (see Table 1).
- Immune complex-related AEs will be defined as any presumptive immune complex-related disorders that are confirmed by an appropriate investigation of the disease and of

complement markers (C3, C4 levels). Clinical manifestations could include skin rash, arthralgia, arthritis, and proteinuria.

The occurrence and duration of each confirmed gout flare will be captured as part of the safety assessments.

3.7.2 Laboratory Evaluations

Clinical laboratory tests such as hematology and blood chemistry panels are not required as part of this protocol. However, a blood sample will be obtained at screening to evaluate G6PD (G6PD deficiency is an exclusion criterion). Blood will also be collected at Visit 1 to establish baseline values for C3, C4, and tryptase. These blood samples will be analyzed by a central laboratory.

Additional blood samples for baseline antibodies to pegloticase and PEG will be drawn and stored frozen. These samples will be tested only for patients who subsequently have an IR, suspected anaphylaxis, or suspected immune complex disease, to be compared with samples obtained at the time of the AE. These antibody analyses will be performed by the designated bioanalytical laboratory.

3.7.3 Vital Signs

Vital signs will consist of pulse rate, sitting blood pressure and body temperature (taken either orally or aurally).

3.7.4 Physical Examination

Physical examinations will be performed by body system at the Screening and Visit 27 or Early Discontinuation Visit. Breast, genitourinary and rectal examinations may be excluded at the discretion of the Investigator.

Significant findings prior to the administration of KRYSTEXXA must be recorded in the patient's medical record and included on the Medical History CRF/eCRF page. Significant findings that occur after administration of KRYSTEXXA which meet the definition of an AE must be recorded in the medical record and on the Adverse Events CRF/eCRF page.

3.7.5 Antibody Formation

For patients experiencing an IR, suspected anaphylaxis, or suspected immune complex disease, both baseline samples and samples obtained at the time of the AE will be assessed by a designated bioanalytical laboratory for the presence of antibodies. Validated enzyme-linked immunosorbant assays (ELISAs) will be performed by the designated bioanalytical laboratory to detect antibodies directed against pegloticase (IgG, IgM and IgE) and against the PEG portion of pegloticase (pan-anti-PEG).

3.8 Adverse Events

3.8.1 Adverse Event Definitions

3.8.1.1 Adverse Event

An AE is any untoward event whether or not considered related to the use of KRYSTEXXA. Any worsening (i.e. any clinically significant adverse change in frequency or intensity) of a preexisting condition which is temporally associated with the use of KRYSTEXXA is also considered an AE. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy, and are recorded on the Adverse Events CRF/eCRF under the signs, symptoms or diagnosis associated with them.

Baseline conditions should not be considered adverse experiences; however, worsening of a pre-existing condition may be considered an AE. Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. An example of this may include, but is not limited to, menopause.

The sponsor will report all AEs according to appropriate health authority (e.g., FDA) guidelines and regulations.

3.8.1.2 Serious Adverse Event

An SAE is any AE occurring that results in any of the following outcomes:

- Death
- Is life-threatening (places the patient, in the view of the Investigator, at immediate risk of death from the event as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if hospitalized as a precautionary measure for continued observation)
- A permanent, persistent or significant disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Is the result of an overdose
- A medically significant event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Events NOT considered to be SAEs are:

- Hospitalization for treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission

- An AE that, had it occurred in a more severe form, might have caused death

3.8.1.3 Adverse Event Classifications

Safety assessments in this study include an evaluation of the frequency and severity of IRs, anaphylaxis, and immune complex-related events. For the purposes of this study, these events shall be defined as follows:

- IRs will be defined as any AE or cluster of AEs, not attributable to another cause, that occurs during or within 2 hours after the infusion of KRYSTEXXA. Other cases that occur outside of the 2-hour window may also be categorized as an IR as per investigator discretion.
- Anaphylaxis will be defined using the NIAID/FANN criteria: acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; swollen lips, tongue, or uvula) **AND** AT LEAST ONE OF THE FOLLOWING:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia
    b. Reduced blood pressure (i.e., systolic blood pressure < 90 mm Hg or greater than 30% decrease from that person's baseline) or associated symptoms of end-organ failure (e.g., hypotonia [collapse], syncope, incontinence)
- Immune complex-related disorders are caused by the deposition of immune complexes in small blood vessels in the body. This can result in the onset of diverse disorders such as glomerulonephritis, skin vasculitis, or arthritis. For the purpose of this study, any presumptive diagnosis of any of these conditions will call for a clinical investigation of the disease and of complement markers (C3, C4). If both the clinical and laboratory investigations are confirmatory, the disorder will be classified as an immune complex-related AE.

3.8.2 Adverse Event Evaluation Criteria

3.8.2.1 Relationship

The determination of the likelihood that KRYSTEXXA caused an AE will be provided by the Investigator. The Investigator's signature and date on the source document and CRF/eCRF that supports the causality noted on the AE form ensures that a medically qualified assessment of causality has been done. The assessment of relationship will be reported by the Investigator according to his/her best clinical judgment. The following scale of criteria may be used as a guidance (not all criteria must be present in order to be indicative of a drug relationship).

Probably related to the drug:

- There is evidence of exposure to the drug
- The temporal sequence of the AE onset relative to administration of the drug is reasonable

- The AE is more likely explained by the drug than by another cause

Possibly related to the drug:

- There is evidence of exposure to the drug
- The temporal sequence of the AE onset relative to administration of the drug is reasonable
- The AE could have been due to another equally likely cause

Unlikely related to the drug:

- There is evidence of exposure to the drug
- There is another more likely cause of the AE
- There is no temporal relationship to the drug

3.8.3 Adverse Event Reporting

Information about all AEs, discovered by Investigator or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event CRF/eCRF and followed as appropriate.

As far as possible, each AE will also be described by:

- its duration (start and end dates)
- its relationship to KRYSTEXXA (unlikely, possibly, or probably)
- the action(s) taken and, as relevant, the outcome

ANY SERIOUS ADVERSE EVENT OR DEATH DUE TO ANY CAUSE THAT OCCURS IN ANY PATIENT IN THIS STUDY, WHETHER OR NOT RELATED TO KRYSTEXXA, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE CONTACT INFORMATION PAGE. ALL PATIENTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

3.9 Adjudication Committees

Two clinical adjudication committees will be established for this study to adjudicate the adverse events reported for events of special interest. The first of these will be a committee comprised of physicians with experience in immunology and allergic reactions. This immunologic adjudication committee will be charged with adjudicating all IRs and cases reported as anaphylaxis to determine if they meet the NIAID/FANN clinical criteria for diagnosing anaphylaxis (see Table 1), based on the described signs and symptoms. Any AEs that have been described as immune-complex related disease will also be evaluated by this expert group, to assess whether the diagnosis has been confirmed by appropriate clinical and laboratory criteria.

In addition, a cardiovascular event adjudication committee, comprised of physicians experienced in this area, will review each potential cardiovascular (CV) adverse event to determine whether or not it meets the diagnosis of a CV event based on established criteria.

3.10 Steering Committee

A protocol Steering Committee will be appointed to periodically review safety reports from the study, as well as the reports from the two independent clinical adjudication committees. The Steering Committee will evaluate these reports and provide assessments to the Savient Senior Management, including the Savient Chief Medical Officer.

4 PROTOCOL AMENDMENTS, OTHER CHANGES IN STUDY CONDUCT

4.1 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment. Unless the changes are designed to eliminate an apparent immediate hazard to patients, both Savient and the governing IRB must grant approval of the amendment before any changes may be implemented in study conduct.

4.2 Other Changes in Study Conduct

Changes in study conduct are not permitted. Any unforeseen changes in study conduct will be recorded in the clinical study report.

5 DATA MANAGEMENT

5.1 Data Collection

Investigators or their designees will enter study data in the CRFs/eCRFs and ensure the data is accurate and complete and that all entries are verifiable with source documents. Study monitors will review data in the CRFs/eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions in a manner compliant with Good Clinical Practice (GCP) guidelines.

5.2 Database Management and Quality Control

Information entered into the database is subjected to systematic logic and consistency checking routines. Obvious errors will be corrected by the appropriate data management personnel in accordance with the data handling and entry guidelines for the study. Findings from the process are reviewed by qualified Data Management or Clinical personnel, after which query forms are returned to the investigational site for resolution of key variables. Each site is expected to respond promptly to data queries. All queries related to AEs must be signed by an investigator. Periodic quality control edit checks of key safety and efficacy data in the database will be made throughout the duration of the study.

Concomitant medications entered into the database will be coded using the World Health Organization Drug Dictionary which classifies according to therapeutic/pharmacological class. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Savient Clinical, Statistical and Data Management Directors.

6 STATISTICAL METHODS

6.1 Statistical Methods

The statistical analysis will be coordinated by the responsible biostatistician. The Statistical Analysis Plan (SAP) will provide additional details on the planned statistical analysis. The SAP will be finalized before the database is locked. Any deviations from the SAP will be described in the clinical study report.

Descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, and maximum) will be used to summarize continuous variables. Descriptive statistics for categorical variables will consist of frequency and percentage.

6.1.1 Population

The analyses will be performed on the Intent-to-Treat (ITT) population. The ITT population will be comprised of all enrolled patients who received at least 1 dose of KRYSTEXXA and have some follow-up data.

6.1.2 Background and Demographic Characteristics

Demographics and other baseline characteristics will be summarized for the ITT population using standard descriptive statistics (number of patients, mean and standard deviation, minimum, median, and maximum), which will be reported and updated for all baseline variables at each data review. All categorical/qualitative data will be presented using absolute and relative frequency counts and percentages. The total number of subjects in the treatment group overall (N) will be used as the denominator for percentage calculations, unless stated otherwise in the SAP. The prediction and profile of the patient's accrual will be made at each review.

6.1.3 Study Medication

Summary statistics for the total exposure to KRYSTEXXA during the treatment period (number of KRYSTEXXA infusions) will be tabulated.

6.1.4 Concomitant Therapy

Concomitant medications will be summarized by therapeutic/pharmacological class. In addition, they will be listed by treatment group, name of drug, dates administered and indication.

6.1.5 Efficacy Evaluation

One efficacy endpoint in this study is normalization of SUA to < 6 mg/dL. Descriptive statistics will be employed to summarize the proportion of responders, where a responder is defined as a patient whose SUA values were < 6 mg/dL at their final 2 consecutive study visits. Summary statistics will be provided for the number of swollen joints and tender joints at baseline, 6 months

(Visit 13) and 12 months (Visit 26) or Early Discontinuation; for changes in numbers of gout flares based on patient reported history at 6-week intervals for Months 1-3 and 3-month intervals thereafter; and for elimination of tophi, i.e., the number of patients with a reported tophus resolution at 6 months (Visit 13) and 12 months (Visit 26) or Early Discontinuation.

It is anticipated that there may be a considerable number of study patients who will drop out of the study. The sponsor will make every effort to identify the reason(s) for dropout before reaching the primary safety endpoint. For the analysis of each efficacy endpoint, various sensitivity analyses will be performed under different assumptions of potentially informative dropouts. For example, in the responder analysis, one analysis will be based on the ITT population with various imputation methods for missing values at the end. Analyses will also be performed assuming all "informative" dropouts are non-responders. For continuous efficacy variables, sensitivity analyses will be performed using standard mixed-effect model repeated measure (MMRM) methods. All the analyses will be summarized using 95% confidence interval estimates. The resulting summarized statistics for efficacy will be compared to those reported from the pre-approval Phase 3 studies.

6.1.6 Safety Evaluation

Adverse events will be summarized by presenting the proportion of patients having any AE, overall and by body system, and by event as defined by the MedDRA preferred term. Separate summary tables will be provided for IRs, anaphylaxis AEs, and immune complex-related AEs.

For each type of the primary safety endpoints, one event, at most, will be counted per patient. The 95% (exact) confidence interval estimates for each type of safety endpoint will be reported for the rate of incidence at the final analysis. The following hypothesis will be specifically tested: the rate of IRs seen in the Phase 3 studies will be reduced in this study by monitoring SUA prior to infusions and discontinuing therapy if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. With at least 500 patients enrolled with 1 year follow-up, the power of detecting a 26% IR rate (the observed value from the pre-approval Phase 3 studies) against 13% is at least 90%. The rate of IRs reported during the study will be reported and compared descriptively to the rates observed in the pre-approval Phase 3 studies.

Descriptive statistics for laboratory values, vital signs, and their changes from baseline will be provided. Safety data will be listed as appropriate. Further details will be specified in the SAP.

6.1.7 Interim Analysis

There is no planned interim analysis. However, the number of enrolled patients will be reassessed approximately 2 years after the first patient is enrolled. This data will be utilized to make a prediction concerning the future enrollment profile. The enrollment goal may be adjusted depending on the drop-out rate such that approximately 500 patients will complete the 1 year treatment period.

6.1.8 Reports to the Adjudication Committees

Periodically, reports of signs and symptoms associated with infusion reactions, cases reported as anaphylaxis, and events described as immune-complex related, will be provided to the clinical immunologic adjudication committee for their review.

Similarly, the cardiovascular adjudication committee will be provided with listings for all serious adverse events and non-serious adverse events with preferred terms that are potentially cardiovascular in nature.

6.2 Sample Size

Approximately 1500 patients will be enrolled in order to observe treatment of up to 500 patients for one year. This target sample size is based on clinical judgment and is thought to be adequate to allow for a robust assessment of key safety and efficacy features. No formal statistical sample size calculation has been performed.

7 PROCEDURES AND INSTRUCTIONS

7.1 Packaging, Labeling, Storage, and Return of Clinical Supplies

KRYSTEXXA® (pegloticase), the reference therapy in this post-market observational study, is commercially available. Please refer to the FDA-approved KRYSTEXXA Full Prescribing Information for specifics regarding handling and storage. Used or unused material may be destroyed at the healthcare facility according to standard institutional procedures. No material should be returned to Savient.

7.2 Drug Administration

7.2.1 Dose Preparation

Visually inspect KRYSTEXXA for particulate matter and discoloration before administration, whenever solution and container permit. Do not use vials if either is present. Use appropriate aseptic technique. Withdraw 1 mL of KRYSTEXXA from the vial into a sterile syringe. Discard any unused portion of product remaining in the vial. Inject into a single 250 mL bag of 0.45% or 0.9% Sodium Chloride Injection, USP for i.v. infusion. Do not mix or dilute with other drugs. Invert the infusion bag containing the dilute KRYSTEXXA solution a number of times to ensure thorough mixing. Do not shake.

KRYSTEXXA diluted in infusion bags is stable for 4 hours at 2°C to 8°C (36°F to 46°F) and at room temperature (20°C to 25°C, 68°F to 77°F). However, it is recommended that the diluted solution be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution. Before administration, allow the diluted solution of KRYSTEXXA to reach room temperature. KRYSTEXXA in a vial or in an i.v. infusion fluid should never be subjected to artificial heating.

7.2.2 Dose Administration

Do not administer as an intravenous push or bolus.

Monitoring Therapy: The risk of anaphylaxis and IRs is higher in patients who have lost therapeutic response. Serum uric acid (SUA) levels will be monitored prior to infusion and therapy will be discontinued if levels increase above 6 mg/dL on two consecutive measurements. If the SUA is noted to be above 6 mg/dl the sponsor suggests that a repeat SUA should be drawn when the result is noted to confirm, and if the 2 consecutive levels are noted to be above 6 mg/dL then it is advised to discontinue therapy.

The KRYSTEXXA admixture should only be administered by i.v. infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. Patients should receive pre-infusion medications (antihistamines and corticosteroids) to minimize the risk of anaphylaxis and IRs. Administer KRYSTEXXA in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and IRs, and observe patients for an appropriate period of time after administration.

Refer to the KRYSTEXXA Full Prescribing Information for management of an IR . Since IRs can occur after completion of the infusion, observation of patients for approximately an hour post-infusion is recommended.

8 REFERENCE LIST

1. Arellano F and Sacristan JA: Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; 27:337-43.
2. Becker MA and Jolly M: Clinical gout and the pathogenesis of hyperuricemia. In: *Arthritis and Allied Conditions, 15th ed* Philadelphia: Lippincott, Williams, and Wilkins 2005: p 2303-40.
3. Chen SM: Serum Sickness. Updated 28 April 2010. WebMD; http://emedicine.medscape.com/article/756444-overview Accessed on 4 Nov 2010.
4. Dalbeth N and Haskard DO: Mechanisms of inflammation in gout. *Rheumatology* 2005; 44:1090-6. Epub 2005 Jun 14.
5. Hande KR, Noone RM, and Stone WJ: Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984; 76:47-56.
6. Kanellis J, Kang D-H, Feig D, and Johnson RJ: Asymptomatic hyperuricemia. In: *Crystal-Induced Arthropathies* (Wortmann RL, et al), New York: Taylor and Francis 2006: p 81-97.
7. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al: Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):391-7.
8. Singer JZ and Wallace SL: The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986; 29:82-7.
9. Stamp L, Gow P, Sharples K, and Raill B: The optimal use of allopurinol: an audit of allopurinol use in South Auckland. *Aust NJ J Med* 2000; 30:567-72.
10. Wu X, Muzny DM, Lee CC, and Caskey CT: Two independent mutational events in the loss of urate oxidase during hominoid evolution. *J Mol Evol* 1992; 34:78-84.

Appendices

Appendix Number	Appendix Title
1	Administrative Procedures
2	Ethics and Good Clinical Practice
3	Schedule of Procedures and Evaluations

Appendix 1: Administrative Procedures

1. Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Savient before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB of all centers. A copy of the written approval of the IRB must be given to the study monitor.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB of each center must be kept informed of such administrative changes.

2. Monitoring Procedures

Investigational sites will be monitored on a regular basis according to vendor monitoring standard operating procedures (SOPs) and study specific monitoring guidelines to assure satisfactory data recording, adherence to the protocol and GCP. The frequency of monitoring may vary depending on enrollment rate and the quantity of data collection, but must occur at least yearly. The Investigator and staff are expected to assist with the study monitor's review of all relevant study documentation, including source documents for each study patient. It is essential that the Investigator and study coordinator set aside a sufficient amount of time for these visits to permit an adequate review of the study's progress and of completed CRFs/eCRFs.

The Investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF/eCRF entries. No information in these records about the identity of the patients will leave the study center.

3. Data Collection

CRFs/eCRFs for the study will be provided. The Investigator or designee must complete the CRFs/eCRFs and transmit the data as instructed at study initiation and must store a copy of the CRF/eCRF with other study documents, e.g. the protocol, the investigators' brochure and any protocol amendments, in a secure place. All entries to the CRFs/eCRFs must be made as described in the CRF/eCRF Completion Instructions or as instructed at study initiation.

Data on patients collected on CRF/eCRFs during the study will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, Savient (and its representatives) and the Investigator are bound to keep this information confidential.

Discrepancies or questions concerning the data will be sent to the Investigator by means of a systematic query resolution process. The discrepancy reports ("queries") should be resolved by

the investigator or study staff, signed and dated, and returned as instructed at study initiation. A copy of the discrepancy report must be retained in the patient binder as a record of changes or acknowledgment of the receipt of queries on the data.

The Investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, etc, and keep the original signed and dated IC form. All information on CRFs/eCRFs must be traceable to these source documents kept in the patient's file. Data obtained without a separate written or electronic source document will be defined before study start and will be recorded directly on the CRFs/eCRFs, which will be documented as being the source data.

4. Document Retention

Essential documents, as listed below, must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after the last marketing approval). Savient will notify the Investigator(s)/institution(s) when the study-related records are no longer required. If the Investigator relocates, retires, or for any reason can not keep the study records, the records may be transferred to an acceptable designee. Savient must be notified in writing of the name, address, and telephone number of the person designated to retain the study records. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include:

- IRB approvals for the study protocol and all amendments
- All source documents including laboratory records
- CRF/eCRF copies
- Data change forms or data queries
- Patients' original signed, dated IC forms (with study number and title of study)
- Monitoring logs and appointment schedules
- Food and Drug Administration (FDA) form 1572 (as required)
- Investigator(s) curriculum vitae, medical license information, and financial disclosure documentation
- All sponsor/investigator correspondence, including telephone logs
- Any other pertinent study document

5. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by Savient (or representatives) in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by Savient or representatives (e.g., protocols, investigators'

brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by Savient or representatives to the Investigator may not be disclosed to others without direct written authorization from Savient. Data generated by this study will be considered confidential by the Investigator except to the extent that it is included in a publication as provided in Appendix 1 Section 6. Publication of results.

Individual patient data obtained during this study are confidential and will not be disclosed to third parties with the following exceptions:

- When data are needed by the patient's personal physician or other medical personnel responsible for the patient's welfare. Prior written consent from the patient or legal guardian must first be obtained.
- For data inspection and verification by Savient or designees (e.g., sponsor's representatives), IRB or regulatory agency representatives.

Individual patient identity cannot be divulged in any communication or publication.

6. Publication of Results

Any formal presentation or publication of data from this study will be considered as a joint publication by the Investigator(s) and appropriate Savient personnel. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication is based on data from all centers that has been analyzed as stipulated in the protocol. Investigators participating in multicenter studies agree not to present data gathered from 1 center or a small group of centers before the full publication, unless formally agreed to by all other Investigators and Savient.

Savient must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). Savient will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplemental information. In accordance with uniform criteria for manuscripts, Savient will impose no impediment, direct or indirect, on publication of the study's full results, including data perceived to be detrimental to the product.

7. Discontinuation of Study

Savient reserves the right to discontinue any study under the conditions specified in the clinical study agreement. In the event that Savient prematurely terminates a particular study site for cause, Savient will promptly notify that site's IRB.

8. Changes in Study Personnel

If there is a change of any personnel listed on the FDA form 1572, a new form reflecting the change must be completed and forwarded to the designated vendor including, when applicable,

any new staff member's signed curriculum vitae, medical license (as appropriate), and signed financial disclosure statement.

Appendix 2: Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with the standard operating procedures of the sponsor's representative for study conduct (contract research organization [CRO]). These requirements are designed to ensure adherence to GCP, as described in:

- International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki (most current version), concerning medical research in humans

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to.

1. Institutional Review Board/Independent Ethics Committee

Before implementing this study and initiating any protocol-related activities, the protocol, the proposed IC form and other information provided to patients must be reviewed by a properly constituted IRB. A copy of the signed and dated statement that the protocol and IC have been approved by the IRB must be sent to the CRO before study initiation. The Investigator must maintain the original approval letter that contains the study number, protocol title, and identification of all documents approved. The Department of Health and Human Services (DHHS) assurance number or statement of compliance with relevant Federal Regulations 21 CFR §56, or the name and occupation of the chairman and the members of the IRB must also be supplied to the CRO. If the Investigator or any member of the study staff is also a member of the IRB, he or she must provide a written statement that he/she absented from voting on this study. Any amendments to the protocol, other than administrative ones, must also be approved by the IRB.

The Investigator must submit annual status reports to the IRB and provide a copy to the CRO. As soon as possible after completion or termination of the study a final report must be submitted to the IRB and the CRO. The Investigator must maintain an accurate and complete record of all submissions made to the IRB including a list of all reports and documents submitted.

The IRB will comply with all federal, state, and local laws. The Investigator will obtain from the IRB and submit to the CRO a signed statement indicating that it complies with GCP. The sponsor (Savient) and the sponsor's representative (CRO) will promptly be advised of any

regulatory inspection relating to this study of either the institution or the IRB. The Investigator will promptly provide a copy of any inspection report.

2. Informed Consent

The Investigator must explain to each patient or patient's legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient or patient's legally authorized representative must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard statement, written in non-technical language. The patient should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before informed consent has been obtained.

The study-specific IC form must be submitted by the Investigator with the protocol for IRB approval. The CRO will supply a proposed IC form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the CRO and Savient, and a copy of the approved version must be provided to the monitor after IRB approval.

3. Compliance with Law, Audit, and Debarment

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, with generally accepted standards of GCP and with all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Investigator also agrees to allow monitoring, audits, IRB review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The Investigator agrees not to seek reimbursement from patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the Investigator by Savient.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations. For each patient participating in the study, the Investigator shall provide all data and submit any other reports to the CRO as required by this protocol or by any other agreement with Savient.

Study documentation will be promptly and fully disclosed to the CRO and Savient by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of Savient or any

regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by Savient as a result of an audit to correct deficiencies in the study documentation and CRF/eCRFs.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will NOT be allowed to conduct or work on Savient studies. The Investigator will immediately disclose in writing to Savient if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

4. Compliance with Financial Disclosure Requirements

By signing this protocol, the Investigator agrees to provide to Savient or their representatives accurate financial information to allow submission of complete and accurate certification and disclosure statements as required by US FDA regulations (21 CFR Part 54). This requirement also extends to subinvestigators.

Appendix 3. Visit Schedules and Assessments

1. Schedule of Procedures and Evaluations

Study Period	**Pre-treatment**	**Treatment Period**					**Follow-up**
Visit	**Screening / Enrollment**	**1 Baseline**	**2-12**	**13**	**14-25**	**26**	**27**
Week	**Up to 2 weeks prior to treatment**	**1**	**3-23**	**25**	**27-49**	**51**	**63**
Procedures							
Informed consent, Medical History, Height and Weight	X						
Physical examination, vital signs	X						X
Gout history and symptom severity	X						
Blood sample for G6PD	X						
Review concomitant medications	X	X	X	X	X	X	X
Initiate gout flare prophylaxis	X						
Acute gout flare assessment		X	X	X	X	X	X
Swollen/tender joint count	X			X		X	
Tophus assessment	X			X		X	
Blood samples to monitor SUA after infusions	X	X	X	X	X	X	
Blood samples for tryptase, antibody and C3 and C4 testing		X					X[1]
Premedicate, obtain vital signs		X	X	X	X	X	
Administer KRYSTEXXA after pre-medicating, monitor infusions		X	X	X	X	X	
Assess for adverse events		X	X	X	X	X	X

Note: C3 = complement component 3; C4 = complement component 4; G6PD = glucose-6-phosphate dehydrogenase; SUA = serum uric acid
X[1] Antibody samples only

2. Schedule of Procedures and Evaluations for Patients in Follow-up after Early KRYSTEXXA Discontinuation

Study Period	**Post-Treatment Period**				
Visit	**4-wks post infusion#**	**3 months post-tx#**	**6 months post-tx***	**9 months post-tx***	**12 months post-tx***
Week					
Procedures					
Physical examination	X				
Review concomitant medications	X	X	X	X	X
Adverse event assessment	X	X	X	X	X
Swollen/tender joint count	X				
Vital signs	X				
Tophus assessment	X				
Blood samples for SUA	X				
Blood samples for antibodies	X	X	X	X	X

All patients continuing in follow-up after early KRYSTEXXA discontinuation will have these visits.

* Patients in post-treatment follow-up after early discontinuation of KRYSTEXXA will be followed only for the planned 1-year duration of their participation. Therefore, depending on when treatment was discontinued for an individual patient, these visits may not be applicable.

3. Serum Sample Collections for Specified Adverse Events

Adverse Event	**Collect serum sample for assessment of:**
Infusion-related AE	Anti-pegloticase, anti-PEG, anti-pegloticase IgE, tryptase, C3, C4
Potential immune-complex AE	Anti-pegloticase, anti-PEG, anti-pegloticase IgE, C3, C4