FDA ARTHRITIS DRUGS ADVISORY COMMITTEE

2 JUNE 2004

BRIEFING DOCUMENT
FOR

OXYPURINOL CAPSULES

NDA 21-740

CARDIOME PHARMA CORP.

EXECUTIVE SUMMARY

Gout is a miserable disease. Acute gout attacks are extremely painful, but fortunately short-lived. Chronic gout can have a very negative impact on quality of life and can be both disabling and deforming. The incidence of gout increases with age and it is largely a disease of older men and postmenopausal women. Patients with gout frequently have other chronic diseases, particularly kidney disease, obesity, and diabetes.

Patients with chronic gout usually benefit significantly from allopurinol treatment. Gout flares are reduced or eliminated, tophaceous deposits are reabsorbed and renal complications are reversed. Unfortunately, approximately 2-4% of patients treated with allopurinol develop a rash or other adverse reaction to allopurinol and must discontinue the medication. These allopurinol-intolerant patients are often without an effective alternate treatment that will lower serum uric acid (SUA) and control their chronic gout symptoms and complications. This small population of patients with chronic gout and intolerance to allopurinol has an unmet medical need and no therapeutic alternatives. Oxypurinol treatment has the potential to benefit approximately 70-75% of these patients. The population that could potentially benefit is estimated to number 7,000 to 14,000 patients in the US.

Oxypurinol is the active metabolite of allopurinol and like allopurinol, is a xanthine oxidase inhibitor. Oxypurinol has been used to treat allopurinol-intolerant patients since 1966 on a compassionate need basis. A pivotal clinical trial of oxypurinol was conducted and showed significant reductions in SUA.

There is little evidence-based literature to assess gout symptoms or severity objectively. There is also a lack of data on quantitative measures to assess the value of therapeutic interventions in chronic gout.

Physiologically, SUA would appear to be a natural measure of therapeutic effectiveness in chronic gout. Uric acid precipitates at approximately 7 mg/dL at 37ºC. Elevated SUA is an important diagnostic measure in chronic gout and a clinical measure that can be monitored during the management of the disease and guide therapy. Observational studies have demonstrated that chronic gout patients have fewer acute gout symptoms when SUA levels are maintained at < 6 mg/dL and that tophi resolve more quickly when SUA is maintained at lower levels.

A prospective, randomized, controlled clinical study has been initiated by Cardiome to evaluate the efficacy of oxypurinol in reducing acute gout symptoms in chronic gout patients who are intolerant to allopurinol. This 2-year study will also evaluate the relationship of SUA reduction to symptom improvement in the chronic gout population and in the significant subgroup of this population with renal impairment.

TABLE OF CONTENTS

TABLES

FIGURES

APPENDICES

1.0 INTRODUCTION

The purpose of this briefing document is to provide the Arthritis Drugs Advisory Committee members with a general overview and background to the science and issues of gout, an outline of the various treatments available, and a discussion of the endpoints, especially the role of serum uric acid (SUA), in clinical trials for new therapies. The use of SUA to measure patient outcomes can be viewed as either a surrogate endpoint or as a primary clinical outcome endpoint. The pros and cons of these approaches will be reviewed to help the committee address the issues that Cardiome Pharma Corp. (Cardiome) believes are critical to any discussion of the future development of new therapies for chronic gout.

Additionally, Cardiome will present data collected with the investigational drug oxypurinol to help illustrate the various issues that will be reviewed. Particular emphasis will be directed to a very small subset of patients with chronic gout who are intolerant to allopurinol. Allopurinol is the major drug used to treat chronic gout patients, and those who are unable to tolerate it represent a group with an unmet medical need for alternate therapy. These patients currently have no effective alternative therapeutic option, but approximately 70-75% of them are able to tolerate oxypurinol.

Cardiome has been in discussions with FDA for several years regarding the development of oxypurinol for the treatment of gout in allopurinol-intolerant patients. Indeed, FDA has been engaged in discussions on this development program for oxypurinol since 1966. Burroughs Wellcome initially filed the IND at that time, but only for compassionate use as a companion to its approved NDA for allopurinol. Oxypurinol IND 3,362 is probably one of, if not the oldest, INDs still active. For most of the 38 years that this drug has been in development, the emphasis has been on compassionate use, first by Burroughs Wellcome, later by Ilex Oncology Inc and most recently by Cardiome. Ilex expanded the program beyond the compassionate use-only stage and initiated Clinical Trial OXPL213. Cardiome acquired the oxypurinol program in 2002, after this study was completed.

2.0 CARDIOME'S PROPOSED INDICATION

Cardiome's NDA proposed the following indication: Oxypurinol is indicated to treat hyperuricemia in patients with symptomatic gout who are intolerant to allopurinol and have failed either rechallenge or desensitization with allopurinol. Oxypurinol should not be used for the treatment of asymptomatic hyperuricemia.

3.0 HISTORICAL OVERVIEW

Gout has been described since the 5th century BC (Kim et al. 2003). Evidence of gouty arthritis is present in the 65 million year old fossil remains of Tyrannosaurus rex (Rothschild, Tanke, and Carpenter 1997). Until the 20th century, gout was often considered a lifestyle disease, associated with excesses of rich food and drink (Figure 1).

Hippocrates first described gout as “the disease of kings” because of its association with a rich diet (Kim et al. 2003).

Figure 1. “By Royal Authority” by George Cruickshank: A Gout Sufferer Helped Onto His Horse.

4.0 PROGRESSION AND SEVERITY OF GOUT

Gout is a metabolic disorder due to hyperuricemia (high SUA levels) and results in the deposition of monosodium urate crystals in the tissues of the body, particularly in the joints and kidneys. Hyperuricemia usually occurs without an obvious cause, but it may also occur as a secondary condition associated with the use of diuretic agents, with renal insufficiency, during the course of starvation or reducing diets and with cyclosporine treatment for organ transplantation. Hyperuricemia can also occur acutely as a result of rapid lysis of tumor masses in the treatment of certain cancers (tumor lysis syndrome).

Gout accounted for a total of 37 million days of restricted activity from 1979 to 1981 in the United States (Roubenoff 1990), and during that period 9.2% of all men with gout were limited in performing major activities. Delayed diagnosis or inappropriate treatment clearly leads to increased morbidity (Ho Jr. and DeNuccio 1993).

Population studies show that gout is associated with increasing steady state serum levels of uric acid (Terkeltaub 2003; Agudelo et al. 2001). Among untreated men with SUA levels in excess of 9 mg/dL, 90% develop gouty arthritis (Hall et al. 1967). Gout is frequently familial in nature and associated with obesity, diabetes, and coronary artery disease (Rott and Agudelo 2003).

The definition of gout using SUA levels follows a physical-chemical law. At concentrations above 7 mg/dL, uric acid crystals form both in vitro and in vivo. Below that level uric acid crystals rarely form. In humans these urate precipitates can present as

tophi (deposits of monosodium urate crystals in the subcutaneous tissues), initially in the extremities. Temperatures in the fingers and toes are slightly lower than in the body's core, permitting urate crystals to form at concentrations slightly less than 7 mg/dL.

Gout is the most common cause of inflammatory arthritis in men aged over 40 years (Kim et al. 2003). Hyperuricemia is defined as SUA levels > 7 mg/dL in men and postmenopausal women, and > 6 mg/dL in premenopausal women (Scott 1983; Hawkins and Rahn 1999; Snaith 1995; McGill 1997). It is a heterogeneous disorder that can progress through several clinical stages if left untreated. These are asymptomatic hyperuricemia, acute recurrent gout, intercritical gout and chronic gout (Harris, Siegel, and Alloway 1999; Van Doormun and Ryan 2000).

Those with elevated SUA levels who do not have clinical signs or symptoms of gout are classified as having "asymptomatic hyperuricemia." This represents a risk factor for gout (and is sometimes considered the first stage). Several studies have linked hyperuricemia with increased cardiac mortality and increased risk of heart disease (Brand, McGee, and Kannel 1985; Hoieggen, Aderman, and Kjeldsen 2004).

In the second stage of the disease referred to as "acute recurrent gout," an acute gout flare occurs as an intense inflammatory response to the deposition of monosodium urate crystals in the joints or in other soft tissues (Pascual 1994; Weinberger 1995). Ninety percent of first attacks of gout are monoarticular (Harris, Siegel, and Alloway 1999), whereas the frequency of polyarticular involvement and the frequency of gout attacks may increase over time (Agarwal 1993). The prevalence of symptomatic gout increases markedly in postmenopausal women, and this group accounts for more than 85% of females who have gout (Ouig et al. 1991; Lally, Ho Jr., and Kaplan 1986).

The third stage, "intercritical gout," is characterized by decreasing intervals between attacks of acute gout. Over time, recurrence of acute gout may become more frequent (three or more attacks of acute gout per year) and polyarticular involvement more common (Agarwal 1993).

In the last stage, "chronic gout," tophi develop, usually after 10 to 20 years of inadequately treated chronic gout (Agarwal 1993). Visible tophi occur in 12% of patients after 5 years and in 55% of patients after 20 years, most commonly in proximity to the elbow and joints of the hands and feet (Wallace and Singer 1988). Tophi are a medically challenging complication of gout. They often cause deformities, damage surrounding soft tissue and lead to joint destruction as well as to chronic, persistent pain and nerve compression syndromes (Hawkins and Rahn 1999) (Figure 2).

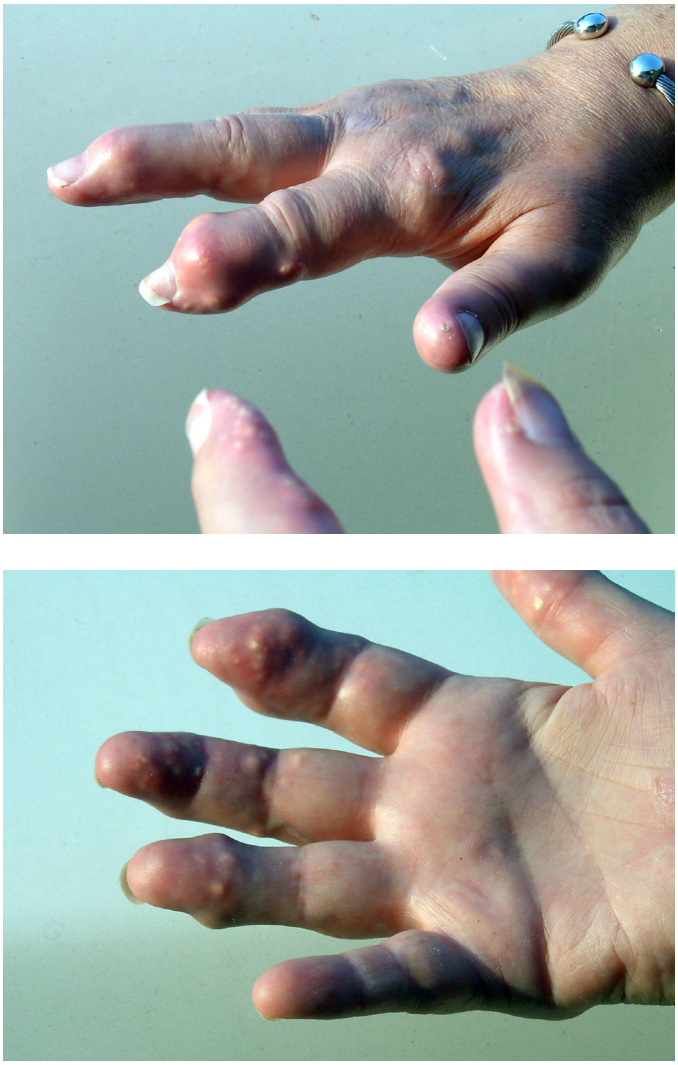


Figure 2. Photographs of a 50-Year-Old Female With Multiple Tophi.

Renal complications of gout may occur in the various phases, but particularly in chronic gout, and include uric acid calculi and chronic urate nephropathy (Kim et al. 2003). Uric acid nephrolithiasis, commonly termed kidney stones, is seen in 10-15% of patients with gout (Reginato and Schumacher 1988). Chronic urate nephropathy occurs more often in patients with chronic tophaceous gout (Agarwal 1993).

5.0 THE MANAGEMENT OF GOUT

Gout has been managed for many people with changes in diet and lifestyle as well as pharmacological intervention. Recommended dietary and lifestyle changes include weight reduction, restriction of alcohol intake, and reduced intake of red meat and seafood. (Choi et al. 2004) Pharmacologic therapy has been developed to treat both the acute inflammation caused by monosodium urate precipitation in joints and to modify uric acid production and excretion in patients with chronic gout.

5.1 Treatment of Acute Gouty Arthritis

5.1.1 Colchicine

Historically, colchicine was the standard treatment for acute gout. While colchicine is often effective in relieving the pain of an acute attack, it frequently causes nausea, vomiting, and diarrhea, and is less widely used today.

5.1.2 NSAIDS

Non-steroidal anti-inflammatory drugs (NSAIDs) have become the treatment of choice for most acute attacks of gout. NSAIDs may also cause significant toxicity, but if used for the short-term, are generally well tolerated.

5.1.3 Corticosteroids

Steroids can be given by intra-articular injection or parenterally and are effective as short-term anti-inflammatory agents. However, significant long-term toxicity precludes chronic use.

5.2 Treatment of Chronic Gout (SUA-Lowering Therapy)

5.2.1 Uricosuric Agents

These agents enhance the excretion of uric acid by the kidneys (Emmerson 1996). Probenecid and sulfinpyrazone are the two uricosuric agents available in the US. Use of uricosurics increases the risk of kidney stones and of renal function impairment. These risks can be minimized by adequate hydration and by alkalinization of the urine. These agents require multiple daily doses and are less effective in patients with diminished renal function.

5.2.2 Xanthine Oxidase Inhibitors

These agents reduce the production of uric acid and are effective in preventing gout and its sequelae. They reduce SUA production by inhibiting the conversion of xanthine to uric acid. Allopurinol is the only FDA-approved xanthine oxidase inhibitor. The urinary excretion of uric acid is also reduced so that the frequency of kidney stones is decreased. Due to its benefit profile and the ease of once daily dosing, allopurinol has become the treatment of choice for chronic symptomatic hyperuricemia.

Oxypurinol, the major metabolite of allopurinol is also an effective inhibitor of xanthine oxidase and is being developed as an alternative treatment for patients who are intolerant to allopurinol.

Table 1 summarizes the roles and effects of current gout therapies.

Table 1: Therapy Options for Gout

	Acute Symptomatic Control	Chronic Symptomatic Control	Reduces SUA
Colchicine	Yes	Partial*	No
NSAIDs	Yes	Partial*	No
Steroids	Yes	Partial*	No
Uricosurics	No	Yes	Yes
Allopurinol	No	Yes	Yes
Oxypurinol	No	Yes	Yes

* Drug used as prophylactic treatment for symptoms associated with recurrent gout attacks

6.0 ALLOPURINOL-INTOLERANT PATIENTS

6.1 Background

The medical need for treatment of allopurinol-intolerant patients with oxypurinol can be illustrated by the history and incidence of allopurinol intolerance. The major limitation of allopurinol resides in its adverse event profile. Two to four percent of patients experience intolerance, which may result in a severe adverse reaction. Shortly after allopurinol was first given to humans for the treatment of hyperuricemia, a pruritic, maculopapular skin rash was reported in some of these early patients. Among 2,394 patients who received allopurinol, 4.4% reported rashes (Wyngaarden et al. 1963).

In most patients, the rash was mildly pruritic, scaling, and/or exfoliative, while in some, more serious reactions were accompanied by fever, malaise, and aching. On average, the rash remitted within 3 days of discontinuation of the drug and could be observed upon rechallenge. It was also noted that most patients experiencing this drug reaction to allopurinol had severe hyperuricemia and renal insufficiency; not all patients with severe hyperuricemia and renal failure had skin eruptions. Of particular importance are the reports of a hypersensitivity reaction characterized by a wide range of dermatological toxicities such as maculopapular, exfoliative, urticarial, or purpuric lesions which may be accompanied by pruritis, chills, fever, and hepatitis (Frish et al. 1975; Hande, Noone, and Stone 1984). Vasculitis, toxic epidermal necrolysis and Stevens-Johnson Syndrome have also been observed. These findings have been corroborated by other investigators (McInnes, Lawson, and Jick 1981; Chalmers et al. 1968).

Zyloprim (allopurinol) prescribing information treats these hypersensitivity reactions very seriously. The package insert states:

"CONTRAINDICATIONS: Patients who have developed a severe reaction to ZYLOPRIM should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions, as well as Stevens-Johnson syndrome (erythema multiforme exudativum), and/or generalized vasculitis, irreversible hepatotoxicity, and, on rare occasions, death." (Zyloprim Prescribing Information 1997)

These allopurinol-intolerant patients are often without effective alternate SUA-lowering treatment for their chronic gout and represent the unmet medical need that Cardiome is attempting to meet with oxypurinol.

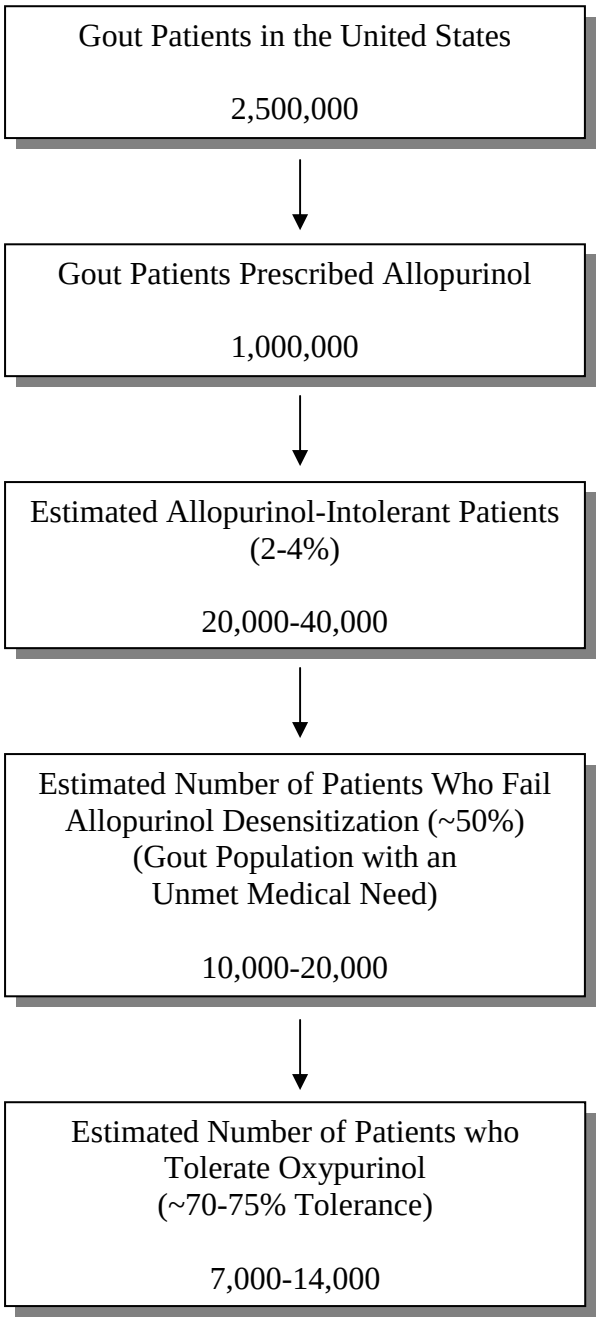
6.2 Treatment of Allopurinol-Intolerant Patients

Allopurinol-intolerant patients have two therapeutic options: allopurinol desensitization or treatment with oxypurinol (Kim et al. 2003; Terkeltaub 2003). Allopurinol desensitization involves the reintroduction of allopurinol at very small doses and the gradual increase in dose to 100 mg per day over a 1-month period. In small open-label studies, desensitization is successful in approximately half of the patients with minor hypersensitivity reactions to allopurinol (Agudelo and Wise 2001; Fam et al. 2001). Allopurinol desensitization is not without risks (Terkeltaub 2003; Unsworth et al. 1987) and has not been universally adopted by the medical community.

6.3 Defining Allopurinol-Intolerant Patients with an Unmet Medical Need

Approximately 2,500,000 gout patients in the US are receiving some form of therapy. Of this group, approximately 1,000,000 are receiving allopurinol (based on IMS data factored from 9.6 million annual prescriptions). Approximately 2-4% of allopurinol-treated patients are intolerant to allopurinol and approximately 50% of these are unable to benefit from allopurinol desensitization. Oxypurinol is tolerated by 70-75% of the remaining population. This population of 7,000 to 14,000 chronic gout patients has no effective alternative therapy and represents an important unmet medical need (Figure 3).

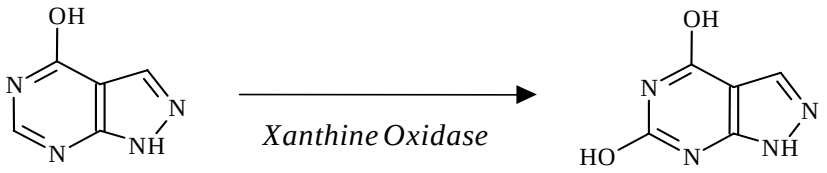
Figure 3. Identification of the Allopurinol-Intolerant Gout Population Potentially Able to Benefit from Oxypurinol.



Legend: Determination of the gout patient population who could potentially benefit from oxypurinol. From a base of 2,500,000 gout patients in the US who are receiving therapy, approximately 1,000,000 are receiving allopurinol (IMS data base factored from 9.6 million prescriptions). Using the estimate of 2-4% intolerance to allopurinol, and allowing for a 50% failure rate from allopurinol desensitization, then approximately 70-75% of the remaining population would potentially receive benefit from oxypurinol (internal Cardiome numbers) and would provide an expected patient population of 7,000 to 14,000 patients.

7.0 OXYPURINOL

Oxypurinol, the primary metabolite of allopurinol, is also an effective xanthine oxidase inhibitor and shares many of the characteristics of allopurinol.



Allopurinol **Oxypurinol**

Figure 4. Allopurinol Metabolism

In healthy volunteers receiving a single 300 mg dose of allopurinol, the half life of oxypurinol was reported to be approximately 16 to 30 hours (Elion et al. 1968; Hande, Noone, and Stone 1984; Lockard et al. 1976), whereas the half life of allopurinol was reported to be 0.5 to 2 hours. This 10-fold difference in half lives is due to the rapid conversion of allopurinol to oxypurinol, and not due to renal elimination. Volume of distribution of both allopurinol and oxypurinol is essentially the same as total body water with neither drug binding significantly to plasma proteins. Only a small amount of allopurinol is excreted in the urine, as almost the entire dose of allopurinol is metabolized. Oxypurinol is largely excreted by the kidney. In patients requiring hemodialysis, oxypurinol has demonstrated clearance by standard 4-hour dialysis.

7.1 Oxypurinol Clinical Development Program

Oxypurinol has been used by patients enrolled in a compassionate use program ongoing since 1966. Patients currently taking oxypurinol in the compassionate use programs have been on treatment for an average of 5.9 years, while one patient has been on oxypurinol for 22 years. These patients take oxypurinol to reduce and control the symptoms of gout. They often have severe symptoms prior to entry into the program and have few or no therapeutic alternatives.

Study CUP 3362-01 was initiated in 1966 to evaluate oxypurinol in allopurinol-intolerant patients. Initially, this was only a compassionate use program. Numerous discussions between prior Sponsors and FDA as well as investigators, clinicians, and patients influenced the direction and scope of the program. With input from all of these stakeholders, a definitive pivotal trial, OXPL213, was conducted. Clinical trial OXPL213 was later modified to be an ongoing compassionate use study, OXPL213-A4, for patients who wanted to continue on oxypurinol after the pivotal trial was completed. Overall, oxypurinol has demonstrated SUA reduction in both sexes, in all adult age groups, in patients with modest or marked SUA elevation and in patients with normal or impaired renal function. Oxypurinol has been granted orphan drug designation.

The clinical studies described in Cardiome's NDA #21-740 and the number of patients enrolled in each study are listed in Table 2.

Table 2: Clinical Studies in the Cardiome NDA #21-740

Study	ID	Total # of patients
Compassionate Use	CUP3362-01	533
Pivotal Phase II	OXPL213	79*
Pivotal Phase II Extension	OXPL213-A4	48
PK I	AAI-US-175	48
Phase IV	OXPL401	240

* Although 79 patients were randomized in the trial, only 77 received study drug and were included in the ITT population

Cardiome and FDA agreed to address the issues identified through the analysis of data from OXPL213, in OXPL401, a Phase IV clinical trial scheduled to begin in June 2004. The protocol highlights chronic gout clinical trial issues of probable interest to the Advisory Committee. These include:

Patient characterization
- the need to demonstrate that the allopurinol intolerant patients are truly allopurinol intolerant.
- the need to demonstrate lack of cross-sensitivity to oxypurinol in allopurinol-intolerant patients

Serum Uric Acid as an Endpoint in Evaluating Clinical Efficacy
- the role of SUA in defining chronic gout
- the role of SUA as a measure of the effectiveness of a drug in the treatment of chronic gout
- the clinical significance of changes in SUA values after treatment with a drug

7.2 Patient Characterization

7.2.1 Characterization of Allopurinol-Intolerant Patients

Chronic gout patients who require treatment with a xanthine oxidase inhibitor have a critical unmet medical need if they are allopurinol-intolerant. Allopurinol intolerance occurs in 2-4% of gout patients, usually as a skin rash (~80%) and less commonly liver enzyme elevations, myelosuppression, or gastro-intestinal upset. Although they may be severe, or even fatal, these adverse events are usually mild or moderate and resolve quickly over several days after discontinuation of allopurinol. While these reactions follow a typical clinical pattern, to be scientifically certain that a particular adverse event is causally related to a drug, re-exposure to the suspect drug is necessary. If the same adverse reaction occurs with repeat exposure and again resolves with discontinuation, this is very compelling evidence that a 'definite' relationship exists between a drug and an adverse event.

All patients who have received, or are currently being treated with oxypurinol have demonstrated a prior intolerance to allopurinol. For the majority, a typical clinical reaction had occurred while taking allopurinol, which resolved when the drug was stopped. In addition, a sizable minority (37%; 225/612) had been re-exposed to allopurinol due to clinical need or during an attempt at allopurinol desensitization. When this confirmed allopurinol-intolerant group was given oxypurinol treatment, 77% (174/225) were able to tolerate oxypurinol treatment without an adverse event considered to be related to oxypurinol. In the allopurinol-intolerant population discussed in Cardiome's NDA #21-740 (612 patients), 75% were able to take oxypurinol without a drug-related adverse event.

Approximately 25-30% of the patients who have been shown to be intolerant to allopurinol also experience an adverse reaction to oxypurinol that precludes their continuing on oxypurinol therapy. These adverse events are generally not severe or serious, but to be conservative, these patients are not permitted to remain on oxypurinol therapy. These adverse events usually occur early in therapy (68% occurred in the first week of treatment in OXPL213) and are identical in more than 90% of cases to the adverse event that the patient experienced on allopurinol. No adverse reactions have been described that are unique to oxypurinol. All adverse reactions likely related to oxypurinol treatment have also occurred in patients taking allopurinol. However, Cardiome recognizes that there may be potential unknown risks for patients who have not had prior oxypurinol therapy. Thus, an extensive risk management program has been devised for oxypurinol to minimize the possibility of patients experiencing serious problems, even though no serious adverse events associated with oxypurinol have occurred during the entire history of the program.

7.2.2 Oxypurinol in Allopurinol-Naïve Patients

In comparison, studies published in the literature demonstrate that when oxypurinol is given to allopurinol-naïve gout patients, the rate of adverse events is much lower than the rate in allopurinol-intolerant patients. In a study of 99 symptomatic hyperuricemic patients given 384 mg of oxypurinol for 14 days, no patient had to stop oxypurinol treatment and only three patients (3%) had adverse events that were probably related to oxypurinol (headache, nausea, and vomiting) (Walter-Sack et al. 1996). In this study, there were no skin rashes in the oxypurinol-treated group. This limited experience with oxypurinol in patients who are not intolerant to allopurinol suggests a low rate of adverse events in this population, which is similar to experience with allopurinol.

8.0 MEASURES OF EFFICACY

Oxypurinol treatment results in a statistically significant reduction in SUA. When introduced at a low dose, for safety reasons, and with gradual dose titration, significant SUA reduction is apparent by 6 weeks. SUA continues to fall over time and averaged 2.87 mg/dL at 1 year in 190 patients in the CUP 3362-01 compassionate use population.

For the OXPL213 trial, the Sponsor (Ilex) and FDA reviewed the literature and the Compassionate Use Program (CUP 3362-01) database and concluded that the primary endpoint should be an average SUA decrease of 2.0 mg/dL. At the time the trial was designed in 1999, it was thought this would be a clinically meaningful endpoint, and if achieved, would also provide the statistical significance needed to support regulatory approval of this orphan drug for the treatment of allopurinol-intolerant patients.

The results of the OXPL213 trial are now available. Indeed, they have been reviewed, analyzed and submitted to FDA in NDA #21-740. Although it demonstrated a highly statistically significant reduction in SUA ($p < 0.0001$), OXPL213 failed to achieve its primary endpoint of an average SUA decrease of 2.0 mg/dL between baseline and Week 14 (the pre-specified statistical endpoint). Overall, the mean decrease found was 1.90 mg/dL; however, this drop was still clearly indicative of significant activity of oxypurinol. The SUA values presented in the NDA reflect the average of Weeks 12-14 for completers but only the last value if patients did not have values in the 12- to 14-week range. Table 3 presents SUA mean change data from OXPL213.

Table 3: Summary of SUA Reductions (mg/dL) in the OXPL213 ITT Population

SUA Evaluation Timepoints	Results
Baseline (N=77)	
Mean	10.11
Median	9.97
SD	1.33
Min, Max	7.7, 13.7
Post- Baseline (N=69)	
Mean	7.96
Median	7.90
SD	1.70
Min, Max	4.4, 12.0
Reduction (N=77)	
Mean	1.90
Median	1.87
SD	1.25
Min, Max	-1.4, 4.2
95% CI	1.61, 2.18
p-value*	< 0.0001

Sensitivity analyses have been used to examine the robustness of these observations based on alternative definitions of change from baseline such as using the last value observed for all patients. This approach unifies the method of endpoint evaluation for all patients. The results of these analyses are discussed in Section 8.3.

8.1 The Role of SUA in Defining Chronic Gout

Elevated SUA is an important diagnostic measure in chronic gout and a clinical measure that can be monitored during the management of the disease. Serum urate precipitates at approximately 7 mg/dL at 37ºC. The precipitates occur throughout the body, but when localized in the joints and the kidneys, they can cause pain, reduce mobility, and interfere with physiological function.

Since the design and completion of the OXPL213 trial, additional information from both the OXPL213 trial and the literature have become available. Darmawan et al. (2003) showed that in a 10-year observational study, with SUA maintained at < 5 mg/dL, control of gout and hyperuricemia was achieved in 91.6% of patients at 2 years, in 87.5% of patients at 5 years, and in 79.6% of patients at 10 years. A study published by Li-Yu et al. (2001) showed that patients who maintained SUA levels of 6 mg/dL for > 12 months had an average of one gout attack a year, while patients who maintained SUA values at > 6 mg/dL averaged six attacks of gout in a 1-year period. Patients with tophi had the most frequent attacks. Perez-Ruiz et al. (2002) found that the speed of tophi reduction was linearly related to the mean SUA level during therapy.

8.2 The Role of SUA as a Measure of the Effectiveness of a Drug in the Treatment of Chronic Gout

Cardiome has designed its Phase IV trial with significant input from FDA, based on clinical data from the oxypurinol development program. Ongoing discussion between FDA and Cardiome has addressed whether SUA can be considered a primary outcome parameter versus that of a surrogate endpoint. At this stage, SUA level can only be considered as a surrogate endpoint. The Phase IV trial may provide data to support SUA as a clinical endpoint.

8.3 The Clinical Significance of Changes in SUA Values after Treatment with a Drug

The intended prospective, randomized, controlled Phase IV clinical trial population was chosen based on the pivotal and supportive data of the OXPL213 and CUP 3362-01 studies, respectively, to focus on those patients most in need of oxypurinol therapy - patients who have displayed intolerance to allopurinol, and then failed a rechallenge or desensitization with allopurinol. This population has no alternate therapy available to lower elevated SUA.

The OXPL213 trial included only patients with a serum creatinine < 2 mg/dL. However, Cardiome's CUP 3362-01 data showed that approximately 38% of the Phase IV population is likely to have at least mild to modest renal insufficiency (serum creatinine 2 mg/dL). The CUP 3362-01 study demonstrated oxypurinol to have clinical value in this population. The Cardiome Phase IV trial does not exclude any patients based on renal function. The titration of doses to bring SUA into the normal range, and assessment of concomitant PK measures will allow Cardiome to study the relationship of outcomes, SUA and dosing, specifically and prospectively, in this important subgroup with renal insufficiency.

Even though the SUA reduction results of OXPL213 are impressive statistically and demonstrated a clear indication of the activity of oxypurinol in this group of patients, the clinical importance of the trial endpoint, a drop of 2.0 mg/dL in SUA, has been questioned. Normalizing SUA may be more relevant than merely measuring a 2 mg/dL fall in SUA that may not lead to a clinically significant treatment effect.

Thus, based on discussions with FDA medical staff, Cardiome looked at the data from the OXPL213 trial from a different perspective. Among the most significant issues is the clinical value of the 2 mg/dL decrease established as the primary endpoint for the trial. While that measure represented an objective endpoint, Cardiome believes an equally meaningful endpoint would have been the return to normal range for the SUA values.

Clinically, the goal of reducing acute gout attacks and chronic tophaceous destruction is guided by therapy aimed at reducing SUA to < 6 mg/dL. It is important to stress that the OXPL213 trial stopped further oxypurinol dose escalation as soon as a SUA reduction of 2 mg/dL had been achieved. In spite of this design limitation, 27 of 54 patients who completed the 14-week trial had a reduction of SUA into the normal range. Cardiome's Phase IV clinical trial specifically titrates oxypurinol dose to a SUA level of < 6 mg/dL and assesses clinical outcome (frequency of acute gout attacks) as the primary efficacy endpoint. Examination of the OXPL213 database demonstrates that 50% (27/54) of the patients who completed the 14-week trial did achieve a reduction of SUA into the normal range of the laboratory for each individual patient. Patient SUA values used to compare to the individual laboratory normal range were the patient's mean value of Weeks 12-14.

Data from this analysis, and for the full ITT population, are presented in Table 4.

Table 4: Proportion of Patients Who Returned to Normal SUA Levels in Trial OXPL213

	Patients Returning to Normal SUA Levels	
Population	**n**	**%**
ITT (n=77)	29	38
Completers (n=54)	27	50

Sensitivity analyses have been used to examine the robustness of these observations based on alternative definitions of falling into the normal range.

Although the original data analysis of OXPL213 performed by Ilex failed to achieve the trial's primary endpoint, when Cardiome presented the full database to its consultant statistician, Dr. Robert W. Makuch of Yale University, he was able to demonstrate three different approaches that he thought should be followed to better appreciate the dataset. The reason he chose different analyses from the original approach is that the original approach gave a zero change score to all patients who dropped out or were discontinued before having a second SUA value, whereas Dr. Makuch thought that it was better not to impute values for SUA but to use all the data that were available. This meant that it was appropriate to conduct a regression test and the data showed a positive change as defined by the primary clinical endpoint.

These additional analyses examined all of the SUA data, without data imputation. Using the full ITT population, The Generalized Linear Models (GLM) approach incorporates the range of 'data completeness' through Week 14, ranging from patients having no post-baseline SUA values to patients having SUA values through Week 14. When the analysis was performed, a statistically significant decline was found between baseline and Week 14 that was greater than the primary endpoint specification of 2.0 mg/dL ($p < 0.001$).

By reexamining the pivotal trial data in several ways including: 1) use of a unified approach based on the final SUA value for all subjects (rather than the protocol-pre-specified average of Weeks 12-14 for the completers and the last value for non-completers), 2) evaluating the proportion of patients who returned to normal SUA levels, and 3) regression analyses that use the full ITT population without any data imputation, it was determined that the three approaches support one another, and reinforce the significant efficacy of oxypurinol. In addition, these analyses support the view that the reduction of SUA values exceeds 2.0 mg/dL, the pre-specified primary endpoint for the OXPL213 trial.

9.0 PHASE IV CLINICAL TRIAL OXPL401

To further assess the efficacy of oxypurinol, a placebo-controlled Phase IV clinical trial will be implemented in June 2004 that will have a treatment duration of 2 years. This trial will evaluate a clinically meaningful endpoint, the number of acute gout attacks per year.

OXPL401 is a Phase IV, double-blind, randomized, placebo-controlled, 2:1 randomization study in 240 allopurinol-intolerant patients. Patients will be titrated to a goal SUA of 6.0 mg/dL or less over a 16-week dose-escalation period. Additionally, those patients with a history of six or more gout attacks a year will be selected, and hence the primary endpoint will be a 50% reduction in gout attacks. Secondary measures will include actual SUA level achieved and size and number of tophi. Thus, for the first time in a controlled clinical study, it will be possible to compare SUA lowering with the clinical outcome of reduction in gout attacks. The protocol for the study is attached as Appendix A.

10.0 RISK MANAGEMENT PROGRAM

Cardiome and FDA have agreed to a risk management (limited access) program that requires patients to be interviewed by physicians and includes a physician and patient education program. Patients must be demonstrated to be allopurinol intolerant and have failed rechallenge with allopurinol. All drug will be supplied by a central mail-order pharmacy.

11.0 CONCLUSIONS

There is a small population of chronic gout sufferers who are allopurinol-intolerant and have an unmet medical need for effective uric acid lowering therapy. Oxypurinol reduces SUA in this population and has the potential to clinically benefit approximately 70-75% of this unfortunate group. Cardiome has proposed a clinical trial to study the relationship between SUA lowering and the control of chronic gout symptoms. Additionally, an extensive risk management program has been developed, focused on patient safety, to ensure that oxypurinol use is restricted to appropriate patients. Providing oxypurinol as a therapeutic option will hopefully allow many chronic gout patients to control their disabling symptoms and return to a more active and pleasurable life.

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Appendix A: Clinical Trial Protocol OXPL401

PROTOCOL

TITLE:	**Oxypurinol for the Treatment of Symptomatic Hyperuricemic Patients Who Are Unable to Tolerate Allopurinol**
PROTOCOL NUMBER:	**OXPL 401**
STUDY DRUG:	**Oxypurinol**
IND:	**3,362**
SPONSOR:	**Cardiome Pharma Corp.** **6190 Agronomy Rd** **6th Floor** **Vancouver, B.C. V6T 1Z3 Canada** **Phone: (604) 677-6905**
DATE OF PROTOCOL:	**30 April 2004**

THIS PROTOCOL IS PROVIDED FOR THE USE OF THE FDA ARTHRITIS DRUGS ADVISORY COMMITTEE AND IS AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

PROTOCOL SIGNATURE PAGE
OXPL 401: Oxypurinol for Treatment of Symptomatic Hyperuricemic Patients Who Are Unable to Tolerate Allopurinol

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Cardiome Pharma Corp. (Cardiome) prior to seeking approval from the Institutional Review Board (IRB) and/or Ethics Committee (EC).

This study will be conducted in accordance with current US FDA regulations, Good Clinical Practices (GCPs), the International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator's Signature: _____

Printed Name: _____

Name of Institution: _____

Date: _____

Sponsor Signature: _____

Garth Dickinson MD, FRCPC

Medical Monitor

Cardiome Pharma Corp.

Date: _____

Please submit a signed copy of this page to Cardiome.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST (SGOT)	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszsel test
CRF	Case Report Form(s)
CUP	compassionate use program
dL	deciliter
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
ECG	electrocardiogram
ESF	Eligibility screening form
GGT	gamma-glutamyl transferase
H	hours
Hgb	hemoglobin
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent to treat
IVRS	Interactive Voice Response System

GLOSSARY OF ABBREVIATIONS

MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSAIDs	Non-steroidal anti-inflammatory drugs
PE	pharmacoeconomic
PK	pharmacokinetic
PP	Per-protocol
PR	pulse rate
QoL	Quality of Life
SAE	Serious Adverse Event
SF-36	36-item short-form health survey
SUA	serum uric acid
ULN	upper limit of normal
WBC	white blood count

TABLE OF CONTENTS

PART I. STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Gout

Gout and its painful, chronic nature were first recorded by Hippocrates in the fifth century BC. Population studies show that gout is associated with increasing steady state serum levels of uric acid [1, 2]. Among untreated men with serum uric acid levels in excess of 9 mg/100mL, 90% develop gouty arthritis [3]. Gout is frequently familial in nature and associated with obesity, diabetes, and coronary artery disease [4].

Colchicine and non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat acute gouty attacks. Uricosuric drugs, particularly probenecid and sulfinpyrazone, have been useful in reducing the blood urate level in patients with gout [5]. However, a risk of uricosuric use is the potential for urolithiasis, particularly in the initial stage of therapy. Uricosuric agents are less effective when renal function is diminished.

1.1.2 Role of Xanthine Oxidase in the Metabolism of Uric Acid

The discovery of the pivotal role of xanthine oxidase in the metabolism of uric acid led to a search for inhibitors of this enzyme. Among the inhibitors discovered were allopurinol and its major metabolite, oxypurinol.

1.1.3 Allopurinol Safety Profile

In one study of 2,394 patients who received allopurinol, 4.4% developed maculopapular or morbilliform dermatologic reactions [6]. In most patients, the reaction was mildly pruritic, with scaling and/or exfoliation, whereas in some, more severe dermatologic reactions were accompanied by fever, malaise, and aching. The rash typically remitted within 3 days of discontinuation of the drug and could be observed on rechallenge. There are reports of a hypersensitivity syndrome characterized by a wide range of dermatologic toxicities such as maculopapular, exfoliative, urticarial, or purpuric lesions which might be accompanied by pruritus, chills, fever, and hepatitis [7]. Vasculitis, toxic epidermal necrolysis, and the Stevens-Johnson syndrome have also been observed.

Since these early observations, numerous other investigators have commented upon these and other related toxicities. Among 29,524 hospitalized patients in the database of the Boston Collaborative Drug Surveillance Program, 1,835 received allopurinol, of whom 65 (3.5%)

reported an adverse effect attributable to the drug. Thirty-two developed allergic skin reactions that may have been caused in part by the concomitant administration of other allergenic drugs. Thirty-three developed nondermatologic toxicity, the most common being hematologic and occurring in 11 patients (0.6%). Thrombocytopenia, leukopenia, hemolytic anemia, and clotting abnormalities were observed [8]. Others have reported instances of agranulocytosis and aplastic anemia. On rare occasions, acute tubular necrosis and interstitial nephritis have been reported. Liver injury may be associated with other manifestations of allopurinol hypersensitivity as noted earlier, or may present as a granulomatous hepatitis.

As with other hyperuricemic therapies, allopurinol treatment may be associated with an increased frequency of acute gouty attacks at the initiation of therapy, presumably as urate stores are mobilized [6]. Allopurinol is known to enhance the incidence of ampicillin-induced rash when administered concomitantly with ampicillin [9].

1.1.4Oxypurinol

Oxypurinol is the primary metabolite of allopurinol and, like allopurinol, is a xanthine oxidase inhibitor. Oxypurinol has been available for compassionate use in allopurinol-intolerant patients since 1966. A total of 533 patients have received oxypurinol under the compassionate use program (CUP) for allopurinol-intolerant patients (Protocol 3,362-01) from its inception through June 30, 2003. An additional 79 patients were enrolled in a clinical trial (OXPL 213), and data were analyzed for 77 patients in the intent-to-treat population of this study. Of these, 48 patients continued into an ongoing compassionate use extension of this trial (OXPL 213-A4). Approximately 150 patients are currently receiving the drug.

Among 210 patients in the 3,362-01 CUP who had a minimum of 14 weeks of oxypurinol therapy and for whom serum uric acid (SUA) measurements were available, the mean SUA significantly decreased by 2.45 mg/dL relative to pretreatment SUA levels ($p < 0.0001$). In this same program, 190 patients on oxypurinol treatment at 1 year had a SUA reduction of 2.87 mg/dL ($p < 0.0001$).

In the OXPL 213 study, the 77 patients in the intent-to-treat population had a 1.90 mg/dL reduction in SUA from baseline after 14 weeks of oxypurinol treatment. This was a highly statistically significant change ($p < 0.0001$) but was less than the predefined primary endpoint for the trial (2 mg/dL). The 54 patients (70.1%) who completed 14 weeks of oxypurinol therapy had an overall mean reduction in SUA from baseline of 2.32 mg/dL ($p < 0.0001$). Most of the therapeutic effect from oxypurinol was evident by 6 weeks when the maximum daily oxypurinol dose was 300 mg. This clinical trial excluded patients with serious renal failure (serum creatinine for entry < 2 mg/dL) and all patients completing the 14 week trial had a daily dose of oxypurinol of at least 300 mg.

Twenty-one of the 79 enrolled allopurinol-intolerant patients (26.6%) discontinued the OXPL 213 study because of oxypurinol-related adverse events. These adverse events

occurred early (68% in the first week of treatment) and were predictable; 90.5% were identical to the adverse event the patient had originally experienced with allopurinol. Most adverse events were mild or moderate in severity, and all resolved with discontinuation of oxypurinol. There were no serious adverse events (SAEs) related to oxypurinol.

Among the 79 patients in the OXPL 213 safety population, 129 treatment-emergent adverse events (AEs) were reported by 57 patients. The most commonly reported AEs were in the skin and subcutaneous tissue body system and were reported by 24.1% of patients. In addition, 13.9%, 11.4%, 10.1%, and 10.1% of patients reported AEs in the gastrointestinal tract, musculoskeletal/connective tissue, metabolic/nutritive disorder, and infections/infestations body systems, respectively.

1.2 Rationale

1.2.1 Rationale for the Study and Study Design

The study will evaluate the long term (2-year) efficacy and safety of oxypurinol in the treatment of symptomatic, hyperuricemic patients with gout. The primary efficacy variable will be a clinical outcome measure – oxypurinol treatment will reduce the number of physician verified acute gout attacks by at least 50% over a 2-year period in comparison to placebo. To assess clinical efficacy, only patients with active gout (six or more acute attacks of gout per year), will be enrolled. All patients will be intolerant to allopurinol as defined by an adverse event, typical of allopurinol intolerance, which subsides with discontinuation of allopurinol and reoccurs with the reintroduction of allopurinol. Reintroduction of allopurinol may occur in the context of a failed attempt at allopurinol desensitization or a clinical rechallenge with allopurinol to assess tolerance.

1.2.2 Rationale for Dosage Selection

Since inception of the oxypurinol compassionate use program in 1966 (Protocol 3,362-01), it has been recommended that oxypurinol dosing begin at low levels (100 mg/day) and that the daily dose be gradually escalated until the desired SUA reduction or clinical improvement has been achieved.

The dose of oxypurinol will be initiated at 100 mg/day for the first 2 weeks of treatment. The dose will be gradually escalated by 100 mg/day every 2 weeks, if indicated. Dose titration will aim to achieve a SUA of < 6 mg/dL and will be supervised by an unblinded 3rd party physician based on adverse events and laboratory data. Patients will be titrated to their individual dose over a total of 16 weeks with a maximal increment of 100 mg every 2 weeks in the daily dosage to a daily maximum of 800 mg. SUA levels will be monitored at each bimonthly visit. Further dose adjustment will be permitted to ensure that the minimally effective dose of oxypurinol is utilized. All doses should be taken with food. Patients will be permitted to take oxypurinol in divided doses (twice daily), if better tolerated (occasional nausea with higher doses).

2. OBJECTIVES OF THE STUDY

2.1 Primary Objectives

To evaluate the efficacy and safety of oxypurinol therapy, over a 2-year period, following a 2 week baseline and 16 week dose titration period, in reducing the number of physician verified, acute attacks of gout in a population of hyperuricemic patients with at least six documented acute gout attacks per year. Patients must be intolerant to allopurinol as documented by a known adverse reaction to allopurinol, which occurred with re-exposure.

2.2 Secondary Objectives:

To evaluate the efficacy of oxypurinol, following dose titration in:

- Reducing total gout flares – physician verified, plus self-reported
- Reducing serum uric acid levels from baseline values
- Reducing serum uric acid levels to < 6 mg/dL
- Reducing size and number of swollen joints
- Reducing size and number of tophi
- Decreasing hospital admissions for gout
- Decreasing emergent clinic visits for gout flares
- Decreasing the frequency of symptomatic nephrolithiasis
- Reducing use of anti-inflammatory and other rescue medications for acute gout flares
- Improving overall quality of life (SF-36)

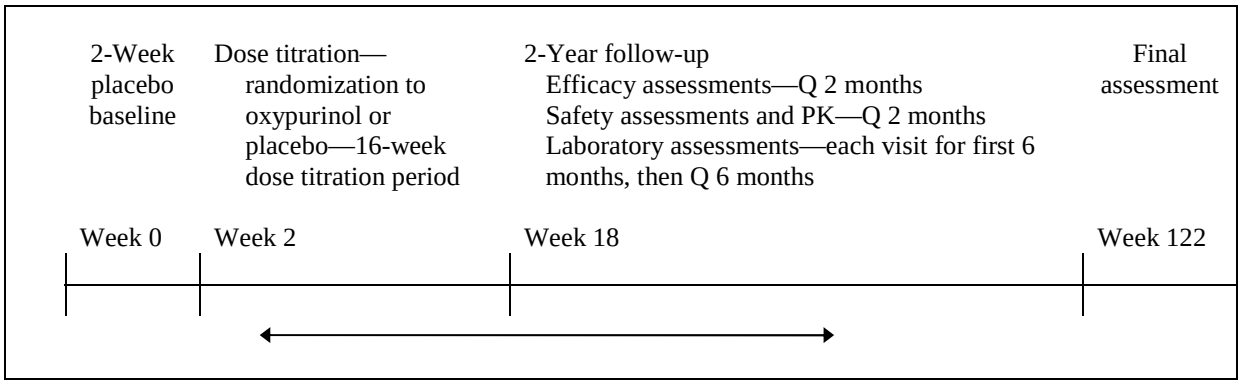
To evaluate the impact of oxypurinol treatment on health care resource utilization (pharmaco-economic assessment)

3. STUDY DESIGN

3.1 Overview of Study Design and Dosing Regimen

Double-blind, placebo-controlled, randomized trial with a duration of 2 years.

- Baseline assessment period of 2 weeks
- Random allocation to oxypurinol or placebo, then 16-week dose titration period
- Monitoring of efficacy and safety parameters for 2 years
- Final assessment at 2 years, 18 weeks



3.2 Number of Patients / Assignment to Treatment

A total of 240 patients are to be enrolled in the study.

Patients will be randomly assigned to receive either oxypurinol or placebo in a 2:1 ratio. The patient randomization numbers will be generated by Cardiome or its designee and incorporated into double-blind labeling.

The patient randomization numbers are to be allocated sequentially in the order in which the patients are enrolled.

3.3 Centers

The study centers will all be in the United States. The number of centers will be based on the available study population. Due to the restrictive definition of the study population, it is anticipated that only a small number of patients will be eligible at any one site. There will be no limitation on the number of patients a single site may enroll. It is anticipated that 80 to 100 centers will participate, each with two or three patients per site.

4. STUDY POPULATION

4.1 Target Population

The target population consists of symptomatic, hyperuricemic patients with active gout, as defined by at least six documented acute gout attacks in the year before enrollment. All patients will be intolerant to allopurinol as defined by an adverse event, typical of allopurinol intolerance, which subsides with discontinuation of allopurinol and reoccurs with the reintroduction of allopurinol. Reintroduction of allopurinol may occur in the context of a failed attempt at allopurinol desensitization or a clinical rechallenge with allopurinol to assess tolerance.

Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study and enrolled for a second course of treatment.

4.2 Inclusion Criteria

- Age between 18 and 80 of either sex.
- Symptomatic gout with at least six documented acute gout attacks in the year preceding enrollment, without effective disease control utilizing other available treatment modalities.
- Hyperuricemia, defined as two or more serum uric acid determinations at least 1 week apart on stable background therapy, which were above the upper limits of institutional normal.
- A history of mild to moderate dermatological or other allergic reactions to allopurinol with recurrence of symptoms on re-exposure to allopurinol.
- Patients must be intolerant to allopurinol as documented by a known adverse reaction to allopurinol, which occurred with re-exposure.
- Patients on other therapy for gout must have been on a stable regime for at least 3 weeks prior to study entry.
- Hematology parameters: Hgb > 10 g/dL (Hgb > 8 g/dL in subjects with a chronic anemia of known etiology that has been stable for > 3 months); WBC > 3000/mm^3; ANC > 1500/ mm^3; platelets > 75,000/ mm^3. Any subject with hematology parameters below the lower limit of normal must have a reasonable clinical explanation for the abnormality and have evidence that the underlying condition has been stable for at least 3 months.
- Biochemical parameters: AST < 2.5 X ULN; ALT < 2.5 X ULN; ALP < 2.5 X ULN; bilirubin < 1.5 X ULN. Any subject with biochemical parameters above the ULN must have a reasonable clinical explanation for the abnormality and have evidence that the underlying condition has been stable for at least 3 months.

4.3 Exclusion Criteria

- Females who are pregnant, lactating or planning on becoming pregnant during the course of the trial.
- Patients who have experienced a severe or serious adverse event related to allopurinol, such as severe exfoliative dermatitis, Stevens-Johnson syndrome, or a serious grade 3 toxicity to any organ system attributed to allopurinol.
- Ongoing alcohol dependence (as per DSM-IV).

4.4 Concomitant Medication and Treatment

4.4.1 Permitted Medications

- Medications used to treat acute gout (analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), cochicine and steroids) are permitted as clinically indicated. Their use must be documented in the CRF.
- Prophylactic medications (NSAIDs or cochicine) to prevent acute gout attacks may be used during the first 6 months of drug treatment, at the discretion of the investigator. Their use must be documented in the CRF.
- Uricosuric agents (probenicid or sulfinpyrazone) are permitted if their dose has been stabilized for at least 3 weeks prior to study entry. Their use must be documented in the CRF.
- Low dose aspirin is permitted if the benefits of treatment are believed to outweigh the risks of increasing SUA. The dose must be stabilized for at least 3 weeks prior to study entry and be documented in the CRF.
- Alcohol consumption should be discouraged.

4.4.2 Excluded medications

- Ampicillin and amoxicillin should not be used due to a possible increased incidence of skin rash.
- Thiazide and loop diuretics (furosemide, bumetanide, ethacrynic acid, torsemide) are excluded because they reduce renal uric acid excretion and increase SUA.

4.5 Patient Discontinuation

- If the patient requests discontinuation
- If a skin rash develops
- If there is evidence of hematologic toxicity as defined by abnormal (> Grade 2 toxicity by the National Cancer Institute of Common Terminology Criteria for Adverse Events v 3.0 (NCI-CTCAE)): Hgb < 8.0 g/dL; WBC < 2000/mm^3; ANC < 1000/ mm^3; platelets > 50,000/ mm^3.
- If there is evidence of hepatic toxicity as defined by abnormal (> Grade 2 toxicity by the NCI-CTCAE v 3.0): AST > 5 X ULN; ALT > 5 X ULN; ALP > 5 X ULN; bilirubin > 3 X ULN.
- If the subject becomes pregnant or fails to use adequate birth control (for those subjects able to conceive).

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Screening Examination and Eligibility Screening Form

An eligibility screening form (ESF) documenting the patient's fulfillment of the entry criteria is to be completed by the investigator for all patients considered for the study, whether they are subsequently included or excluded, and forwarded to Cardiome. Screening will include fulfillment of all inclusion and but no exclusion criteria. Documentation of gout severity criteria, SUA and allopurinol intolerance and rechallenge are particularly important.

5.2 Study Assessments

The schedule of assessments is shown in Table 5.2-1.

Table 5.2-1 Schedule of Assessments

	Screen Week	Baseline Week		Titration Period (Week)*								Treatment Period (Months)												Final Assessment (or discontinuation)
Study Day	0	1	2	4	6	8	10	12	14	16	18	6	8	10	12	14	16	18	20	22	24	26	28	30 Months
Informed Consent	X																							
Demographics	X																							
Medical History & Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X																							
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Physical Measurements	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Uric Acid* (SUA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[1]	X			X	X	X	X	X	X	X	X	X			X			X			X			X
Renal Function[2]	X			X	X	X	X	X	X	X	X	X			X			X			X			X
Liver Function Tests[3]	X			X	X	X	X	X	X	X	X	X			X			X			X			X
PK Samples				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36 (QoL)	X										X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose Adjustment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

*SUA blood levels should be drawn 1 week after starting a treatment dose and 1 week before the next assessment

[1] Hgb, WBC with differential, platelets; [2] creatinine, urea; [3] AST, ALT, ALP, GGT, bilirubin

5.2.1 Clinical Assessments

- Number of acute gout attacks
- Size and number of swollen joints
- Size and number of tophi
- Episodes of symptomatic nephrolithiasis
- Compliance with study medication
- Hospital admissions for gout
- Emergent clinic visits for gout flares
- Use of anti-inflammatory and other rescue medications for acute gout flares
- Adverse events

The primary endpoint will assess only physician verified acute gout attacks, following the dose titration period. An acute gout attack is defined as the development of an acutely painful joint, typical of acute gout, which requires therapeutic intervention. Physician verified attacks must be assessed and documented by an investigator or by another physician. When a non-investigator physician assesses the patient (as in a clinic or an emergency department), the Clinical Events Committee will adjudicate whether the patient visit was the result of an acute gout attack, based on the available clinical documentation.

5.2.2 Laboratory Assessments

- SUA
- Renal function (creatinine, urea), liver function tests (AST, ALT, ALP, GGT, bilirubin), complete blood count (Hgb, WBC, with differential, platelet count)

5.2.3 Pharmacokinetic Assessments

Steady state (pre-dose) oxypurinol blood levels will be assessed at every visit (both scheduled and unscheduled) for the duration of the study. The effects of dose, age, sex, ethnicity, renal and hepatic impairment on steady state blood levels will be assessed.

5.2.4 Quality-of-Life Assessments

- SF-36 Quality-of-Life Questionnaire

The SF-36 Quality-of-Life Questionnaire is a multipurpose short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures and a

preference-based health utility index. It is a widely used, validated and generic measure of disease burden and overall health status.

5.2.5 Pharmacoeconomic Assessments

Comparisons of costs of treatment, including costs of rescue medications, medical visits, hospitalizations, lost productivity, and adverse events between active treatment and placebo groups. A more detailed pharmacoeconomic assessment plan will be developed.

6. INVESTIGATIONAL PRODUCT

6.1 Dose and Schedule of Oxypurinol and Placebo

The first 2 treatment weeks are a blinded placebo treatment in all patients. Patients are then randomized to receive either oxypurinol or placebo, in a 2:1 ratio until the end of the trial. Serum uric acid levels will then be assessed in all patients in a blinded fashion weekly during the 16-week titration period.

The dose of oxypurinol will be initiated at 100 mg/day for the first 2 weeks of treatment. The dose will be gradually escalated by 100 mg/day every 2 weeks, if indicated. Dose titration will aim to achieve a SUA of < 6 mg/dL and will be supervised by an unblinded 3rd party physician based on adverse events and laboratory data. Each patient will be titrated to his or her individual dose over a total of 16 weeks with a maximal bi-weekly increment of 100 mg in the daily dosage to a daily maximum of 800 mg. SUA levels will be monitored at each bimonthly visit. Further dose adjustment to a maximum of 800 mg per day will be permitted to ensure that the minimally effective dose of oxypurinol is utilized. All doses should be taken with food. Patients will be permitted to take oxypurinol in divided doses (twice daily), if better tolerated (less nausea).

Each patient on placebo will also have his or her 'dose' titration supervised by an unblinded 3rd party physician to match the dose adjustments in the oxypurinol group (see Section 10.3).

6.2 Preparation and Administration of Oxypurinol and Placebo

Oxypurinol and placebo will be supplied in identical opaque white capsules.

Details of formulation, packaging and labeling are described in the Study Procedures and Administrative Manual.

6.3 Blinding and Randomization

A computer-generated randomization list will be generated by an independent biostatistician. The randomization list will not be available at the study center, to the Cardiome monitors, project statisticians or to the project team at Cardiome. If knowledge of the identity of the test medication is necessary for either patient management (in the case of a serious adverse event) or independent pharmacological analysis of biological samples, procedures for ensuring integrity of the data will be followed, as detailed in the *Study Procedures and Administrative Manual*.

Randomization will be in blocks of three (2 oxypurinol and 1 placebo). Randomization will occur through the use of an Interactive Voice Response System (IVRS) and patients will be assigned to treatment in the order they are enrolled. Once assigned, a randomization number will not be reused. Each placebo patient will be matched with an oxypurinol treated patient at a different site. Every dose adjustment (increase or decrease) which occurs with the oxypurinol treated patient will be matched by an identical dose adjustment (increase or decrease) in the placebo treated patient. This will create the appearance of a single treatment group and will maintain the blind.

Patients, principal investigators, and Cardiome project staff will all be blinded to SUA assessments. Cardiome will select an independent unblinded medical monitor to assess patient SUA levels throughout the trial. The unblinded medical monitor will be responsible for providing dose regimen changes for study subjects determined by their SUA levels. To protect the study blind, the sham dosing strategy described above will be used for patients randomized to receive placebo.

6.4 Compliance

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Further details can be found in the Study Procedures and Administrative Manual.

7. SAFETY ISSUES

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen during a study are to be reported as AEs.

All AEs encountered during the clinical study will be reported on the AE page of the case report form (CRF). **Intensity** of adverse events will be graded on a four-point scale (mild, moderate, severe, life-threatening) as described below, and will be reported in detail as indicated on the CRF.

Rating scale for **intensity** of adverse events:

Mild:	Discomfort noticed but no disruption of normal daily activity
Moderate:	Discomfort sufficient to reduce or affect daily activity
Severe:	Inability to work or perform normal daily activity
Life threatening:	Represents an immediate threat to life

Relationship of the adverse event to the treatment should also be assessed. Description of scales can be found in Appendix 1.

7.1.2 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable. Laboratory test value abnormalities as such should not be reported on the AE page of the CRF as adverse events, unless there is an associated clinical condition for which the patient is given treatment or concomitant treatment altered, it is considered to be a serious adverse event, or the subject is permanently discontinued from study drug because of the abnormal test value.

7.2 Handling of Safety Parameters

7.2.1 Serious Adverse Events (Immediately Reportable to Cardiome)

Any clinical adverse event or abnormal laboratory test value that is ***serious*** occurring during the course of the study, irrespective of the treatment received by the patient, must be reported to Cardiome within *one* working day of knowledge.

For each AE, you must determine if it is a serious adverse event (SAE) according to the following definition.

An SAE is an AE, occurring at any dose, which fulfills one or more of the following criteria: (1) results in death, (2) is immediately life-threatening, (3) requires in-patient hospitalization or prolongs an existing hospitalization, (4) results in persistent or significant disability or incapacity, (5) is a congenital abnormality/birth defect, or

(6) is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Please refer to Appendix 2 for further explanation and examples.

YOU MUST REPORT ANY SAE, INCLUDING DEATH DUE TO ANY CAUSE, WITHIN 24 HOURS. COMPLETE THE SAE REPORT FORM AND SEND TO:

Cardiome Safety
FAX # 604 676 6970
Phone # 604 677 6905

YOU MUST FOLLOW ALL PATIENTS WITH A SAE, INCLUDING PATIENTS DISCONTINUED FROM STUDY MEDICATION, UNTIL THE RESOLUTION OF THE ADVERSE EVENT

The definition and reporting requirements of the *ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2* will be adhered to. Complete information can be found in Appendix 2.

7.2.2Treatment and Follow-up of Adverse Events

Adverse events, especially those related to study drug, should be followed up until they have returned to baseline status or stabilized. If a clear explanation is established it should be recorded on the CRF.

7.2.3Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

7.2.4Pregnancy

A female patient must be instructed to stop taking the test drug and immediately inform the investigator if she becomes pregnant during the study. Pregnancies occurring up to 90 days after the completion of the study drug must also be reported to the investigator. The investigator should report all pregnancies within 24 hours to the sponsor. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a patient participating in the study should also be reported to the investigator and the sponsor. The partner should be counseled and followed as described above.

7.3 Dose Modifications for Toxicity

At the first sign of a skin rash or other adverse event that may be possibly related to oxypurinol, the patient should discontinue study medication and consult with the investigator. If the investigator believes that the adverse event is clinically significant and likely related to study drug, then the study drug should be discontinued and the patient should be withdrawn from the trial.

7.4 Criteria for Premature Withdrawal

Subjects have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violations, cure, administrative reasons or other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

The investigator should contact the subject either by telephone or through a personal visit, or a responsible relative must be contacted to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

Warnings and Precautions

No evidence available at the time of the implementation of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Study Endpoints

8.1.1 Efficacy Endpoints

8.1.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the number of documented physician verified acute gout attacks, requiring additional treatment and reported by the patient to the investigator, during the 2-year study period which follows the 2-week baseline and 16-week dose titration periods.

8.1.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be examined after dose titration;

- Total number of gout flares – physician verified, plus self-reported
- Reduction in SUA from baseline
- Proportion of patients with SUA levels < 6mg/dL
- Size of swollen joints
- Number of swollen joints
- Size of tophi
- Number of tophi
- Number of hospital admissions for gout
- Number of emergency room visits for gout flares
- Number of episodes of symptomatic nephrolithiasis
- Use of anti-inflammatory and other rescue medications for acute gout flares
- Responses to the SF-36 Quality-of-Life Questionnaire

8.1.2 Safety Endpoints

Safety will be assessed by the following endpoints;

- Adverse events,
- Vital signs,
- Laboratory data (CBC, Renal function, Liver function tests, and SUA).

8.2 Statistical and Analytical Methods

8.2.1 Hypothesis Testing

All statistical tests will be two-sided with a significance level of 0.05. No adjustment of p-values will be performed since there is one primary efficacy endpoint.

The test for superiority of oxypurinol versus placebo will be based on the following null hypothesis and alternative hypothesis;

$$H_o: \mu_{Oxypurinol} = \mu_{placebo}$$

$$H_a: \mu_{Oxypurinol} \neq \mu_{placebo},$$

where $\mu_{Oxypurinol}$ and $\mu_{placebo}$ are the mean number of documented physician verified acute gout attacks requiring additional treatment and reported by the patient to the investigator during the 2-year study period for the oxypurinol and placebo groups, respectively.

8.2.2Sample Size

The sample size calculation for this study is based on the clinical assumption that oxypurinol will reduce the frequency of gout attacks by at least 50% (i.e. from six attacks to three attacks per year over the 2-year study period). Assuming a common standard deviation of 3, a total of 192 patients, using a 2:1 randomization schema (128 oxypurinol, 64 placebo) are required to achieve 90% power to be able to detect a minimum difference of 1.5 gout attacks. This is based on a 2-sided t-test with a 5% significance level.

Allowing for a potential 25% drop out rate during the first 16 weeks of the study the sample size for the protocol is estimated at 160 patients in the oxypurinol group and 80 patients in the placebo group for a total sample size of 240 patients.

8.2.3Analysis Populations

Intent-To-Treat (ITT) Population – The ITT population will be used for the primary analysis of efficacy. This population will include all patients who are randomized and receive at least one dose of study medication and complete the 18 week titration period.

Per-protocol (PP) Population – The PP population will provide support for the primary efficacy analysis and will include all patients in the ITT population who have no major protocol violation, have completed the 2 years of the study. Major protocol violations will be identified prior to treatment blind being broken, and may include, but are not limited to, significant violation of inclusion/exclusion criteria, and noncompliance with study medication.

Safety Population – The safety population will include all patients who received at least one dose of study medication.

8.2.4 Efficacy Analyses

8.2.4.1 Primary Efficacy Analysis

The primary efficacy analysis will consist of a comparison between the mean number of documented physician verified acute gout attacks (requiring additional treatment and reported by the patient to the investigator, during the 2-year study period) between the oxypurinol and placebo groups. This analysis will be based on a general linear model with fixed effects for treatment and center. The lsmeans, standard error of the lsmeans, difference in lsmeans, standard error of the difference in lsmeans, 95% confidence interval of the difference in lsmeans and p-value for the difference in lsmeans will be reported. If the assumption of the general linear model are severely violated, analogous non-parametric techniques will be used.

8.2.4.2 Secondary Efficacy Analyses

Secondary analysis of continuous and discrete secondary efficacy endpoints will utilize methods outlined under the primary efficacy analysis.

For categorical data, comparisons between the oxypurinol and placebo group will be based on the Cochran-Mantel-Haenszsel (CMH) test, stratified by center. If warranted, Fisher's Exact test will be used. The following statistics will be presented; frequency and percentages of each category by treatment group, the difference between treatment groups along with the 95% confidence interval of the difference (for binary variables), and the p-value for the difference between treatment groups.

8.2.4.3 Exploratory Efficacy Analyses

Exploratory efficacy analyses will be performed on the Per-protocol population for all measures of efficacy at the end of the titration period, after 6 months, 1 year and 2 years of treatment. Further exploratory efficacy analyses will be performed on the Per-protocol population in relation to final dose level of oxypurinol, initial serum creatinine and nature of allopurinol intolerance.

8.2.5 Safety Analyses

8.2.5.1 Adverse Events

All adverse events will be coded using MedDRA terminology. Adverse events summarized in tables will be treatment emergent adverse events that are defined for each individual patient as an event not present prior to beginning study medication, or, if present prior to beginning study medication, an event which increases in intensity, is considered related to the study medication, or becomes serious during the treatment or follow-up phases of the study.

The following summaries will be presented for treatment emergent adverse events by treatment group and preferred term;

- Adverse Events by Body System (All causalities)
- Adverse Events by Body System and severity (All causalities)
- Adverse Events by Body System (Treatment Related)
- Adverse Events by Body System and Severity (Treatment Related)
- Adverse Events by Body System, Severity and Relationship (All causalities)
- Adverse Events causing Withdrawal by Body System and Relationship (All causalities)
- Serious Adverse Events by Body System and Relationship (All causalities)

8.2.5.2 Vital Signs

Vital signs will be summarized (mean, standard deviation, median, minimum, maximum) by treatment group at each time point. Additionally, the change from baseline to each time point will be summarized (mean, standard deviation, median, minimum, maximum) by treatment group. Comparisons for the median change from baseline will be made for each time point using the Wilcoxon test.

8.2.5.3 Laboratory Parameters

Summary statistics (mean, standard deviation, median, minimum, and maximum) for all laboratory parameters will be presented for each time point by treatment group. Additionally, the change from baseline to each time point will be summarized (mean, standard deviation, median, minimum, and maximum) by treatment group. Comparisons for the median change from baseline will be made for each time point using the Wilcoxon test.

Summary statistics (frequency counts and percentage) by treatment group for the number of patients with low, normal, and high lab values will be presented for each time point, compared to baseline, using shift tables.

8.2.6 Other Analyses

8.2.6.1 Pharmacokinetic Analysis

Steady state (pre-dose) oxypurinol blood levels will be assessed at every visit (both scheduled and unscheduled) for the duration of the study. The effects of dose, age, sex, ethnicity, renal and hepatic impairment on steady state blood levels will be assessed.

The relationship between steady state oxypurinol blood levels and SUA reduction and the incidence of AEs will be determined.

8.2.6.2 Pharmacoeconomic Analysis

Analysis of pharmacoeconomic data and production of a final pharmacoeconomic report will be handled separately from the final clinical report of this study. Information obtained from the collection of medical care utilization data in this study may be combined with other data such as cost data or other clinical parameters in the production of a final pharmacoeconomic analysis report.

8.2.7 Disposition

The number of patients enrolled in the study, evaluability status, reasons for nonevaluability, reasons for discontinuation, and duration of treatment (drug exposure) will be summarized in tabular format by treatment group.

8.2.8 Demographics and Baseline Analysis

Baseline and demographic characteristics measured at screening/baseline on all participants will be compared between treatment groups. For continuous measures, mean, standard deviation, median, minimum and maximum will be provided and for categorical variables, counts and percents will be provided. Comparisons will be made between groups using a general linear model, with fixed effects for treatment and center, for continuous variables and the Cochran-Mantel-Haenszsel (CMH) test, stratified by center, (or Fisher's Exact tests where appropriate) for categorical variables.

8.2.9 Concomitant Medications

Concomitant medications used during the study will be summarized by treatment group.

8.3 Interim Analysis

There is no planned interim analysis.

8.4 Replacement Policy (Ensuring Adequate Numbers of Evaluable Patients)

8.4.1 Patients

No patient prematurely discontinued from the study for any reason will be replaced.

8.4.2 Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence

9. DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross–check of the CRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.

The data collected will be entered into the study database from the working copy of the CRF faxed from the site.

A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator. As patients complete the study (or prematurely withdraw) and their signed CRFs become available, a second data entry will be performed from the original, signed CRF. A comparison check will be run to identify and resolve any discrepancies between the first and second data entry.

Throughout the study the Study Management Team will review data according to its Data Review Plan as described in the Data Quality Plan.

10. STUDY COMMITTEES

10.1 Steering Committee

Cardiome will select Steering Committee members and a chairperson to represent the sponsor in the management of this trial.

10.2 Clinical Events Committee (CEC)

The CEC will be made up of members with expertise in the management of hyperuricemic patients. They may or may not be investigators in this trial. The CEC will be responsible for adjudicating cause of hospital admissions and emergent clinic visit for gout flares as well as episodes of symptomatic nephrolithiasis.

10.3 Unblinded Medical Monitor

Cardiome will select an independent unblinded medical monitor to assess patient SUA levels throughout the trial. The unblinded medical monitor will be responsible for providing dose regimen changes for study subjects determined by their SUA levels.

To protect the study blind a sham dosing schedule will be included for patients randomized to receive placebo. All dose modifications will be by 100 mg daily increments. Each placebo patient will be matched with an oxypurinol-treated patient at a different site. Every dose adjustment (increase or decrease) that occurs with the oxypurinol treated patient will be matched by an identical dose adjustment (increase or decrease) in the placebo treated patient. This will create the appearance of a single treatment group and will maintain the blind.

11. REFERENCES

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the USA or under a US IND, the investigator will additionally ensure that the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards", are adhered to.

In other countries where guidelines for good clinical practice exist, Cardiome and the investigators will ensure strict adherence to the stated provisions.

12.1.1 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The final informed consent form must be approved by the appropriate Institutional Review Board (IRB) and accepted by Cardiome. The consent form must reflect the required elements of informed consent specified in 21 CFR Part 50.25 and 45 CFR Part 164.508 (HIPAA). If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, be given a copy of the revised form, and should give their consent to continue in the study.

12.1.2 Institutional Review Board

It is the understanding of the sponsor that this protocol (and any modifications), as well as appropriate consent procedures, and the Investigators Brochure will be reviewed and

approved by an IRB. This board must operate in accordance with the current Federal Regulations. The investigator will send a letter or certificate of approval to the sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made. If the duration of the study is greater than 1 year, re-approval by the IRB must be obtained on a yearly basis (or at more frequent intervals if required by the IRB).

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Project Director and Medical Monitor.

All protocol modifications must be submitted to the appropriate IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. IRB approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s).

14. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Cardiome and the investigator will assure that adequate consideration is given to the protection of the subject's interests.

15. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Investigator Brochure, Case Report and Query Forms, IRB approval with correspondence, IRB membership list, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, x-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs. The Investigator must keep these two categories of documents on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

If the Investigator can not guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Cardiome to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

15.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Cardiome Research Quality Assurance Unit or its designees, or to health authority inspectors after appropriate notification. The verification of the Case Report Form data must be by direct inspection of source documents.

15.4 Case Report Forms

For each patient enrolled, a CRF must be completed and signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

All forms should be typed or filled out using black or blue indelible ink, and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

16. MONITORING THE STUDY

It is understood that the responsible Cardiome monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements. The first visit to the site will be completed prior to patients being enrolled into the trial. During this visit the monitor will review the protocol and study expectations with the site.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. A closeout visit will be scheduled after the last subject has completed participation in the study. The investigator may be asked to provide additional information to support the clarification and/or correction of clinical data entries after the site has been closed.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses. Log sheets containing patient identifying information should be kept in a separate location from other study documentation. The investigator should maintain documents not for submission to Cardiome, e.g., subjects' written consent forms, in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Cardiome prior to submission. This allows the sponsor to protect proprietary information and to provide

comments based on information from other studies that may not yet be available to the investigator.

In accord with standard editorial and ethical practice, Cardiome will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Cardiome personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Cardiome personnel. Authorship will be determined by mutual agreement.

19. STUDY ORGANIZATION AND ADMINISTRATION

Cardiome is the study sponsor, and retains the legal responsibility for all responsibilities not officially delegated to contracting entities. Cardiome management team is made up of the Project Director, Medical Director, and the VP of Clinical Development and Medical Affairs. The management team has the responsibility for all operational aspects of the study and all day-to-day operations of the trial, including investigator identification, investigator interactions, safety monitoring and reporting and data management and reporting.

Appendix 1 Adverse Events Categories for Determining Relationship to Test Drug

The categories describing the relationship of an adverse event to the test drug are summarized in Table A.1 below.

Table A.1 Summary of Relationship of an Adverse Event to the Test Drug

Category	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	–	–	–	+
Reasonable temporal association with drug administration	+	+	–	–
May be produced by subject clinical state, etc.	–	+	+	+
Known response pattern to suspected drug	+	+	–	–
Disappears or decreases on cessation or reduction in dose	+	–	–	–
Reappears on rechallenge	+	–	–	–

PROBABLE (must have first three)

This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered probable, if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; eg, (1) bone marrow depression, (2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug.
5. It reappears upon rechallenge.

POSSIBLE (must have first two)

This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

3. It follows a known pattern of response to the suspected drug.

REMOTE (must have first two)

In general, this category is applicable to an adverse event which meets the following criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

UNRELATED

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under remote, possible, or probable.

Appendix 2 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

- Fatal; (results in death)
  NOTE: Death is an outcome, not an event.
- Life-threatening
  NOTE: The term "life-threatening event" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.
- Required in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected adverse event is an event whose nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For serious adverse events, causality can be one of 2 possibilities:

- No (unrelated; equals not drug related)
- Yes (remotely, possibly, probably or definitely drug related)

The term severe is a measure of intensity, thus a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.