NDA 21-740 - OXYPRIM™
Arthritis Advisory Committee Briefing Document
June 2, 2004

Name:	Oxypurinol
Proposed trade name:	Oxyprim™
Drug Class:	Xanthine oxidase inhibitor
Sponsor:	Cardiome Pharma Corp
Indication:	Hyperuricemia in patients with symptomatic gout who are intolerant to allopurinol and have failed either rechallenge or desensitization with allopurinol
Dosage form/route:	100 mg oral hard gelatin capsules.
Dose:	300 mg to 800 mg daily
Type of application:	Application has been given Priority Review status. It has been submitted under Subpart H: - Uses of a surrogate marker as primary evidence of efficacy: change in serum uric acid (SUA) levels. - Requires a risk/management program (RMP)

DISCLAIMER: This is the preliminary summary of an ongoing review.

Background information

Oxypurinol is the major metabolite of allopurinol. Both allopurinol and oxypurinol inhibit the synthesis of uric acid by action on the enzyme xanthine oxidase. Allopurinol effectively reduces serum uric acid (SUA) levels and is generally well tolerated. Target therapeutic long-term levels for SUA are < 6 mg/dl. However, others advocate that the optimal SUA is < 5 mg/dl. According to the literature, at least 2% of patients develop hypersensitivity reactions to allopurinol, and 20% of those are severe. Severe reactions include rashes such as toxic epidermal necrolysis, hepatitis, interstitial nephritis, and death.

Oxypurinol was not originally developed as a therapeutic agent for gout because it has less inhibitory activity (on a molar basis) against xanthine oxidase than allopurinol. However, oxypurinol has been available to patients with allopurinol intolerance under a compassionate protocol since 1966 (IND 3,362). According to the literature, up to 40% of patients treated with oxypurinol develop allergic reactions similar to those of allopurinol.

Negotiations between a prior sponsor (ILEX Corp.) and the DAAODP regarding the possibility of marketing oxypurinol started in 1997. The current application and NDA is being submitted by Cardiome Pharma Co. Cardiome maintains that oxypurinol is effective in reducing SUA levels and has the advantage of being safer than allopurinol in terms of overall hypersensitivity reactions. Cardiome intends to market Oxyprim™ for the treatment of hyperuricemia in patients with symptomatic gout, intolerant to allopurinol. (See attached articles on hyperuricemia, gout, hypersensitivity reactions to allopurinol and the allopurinol desensitization regimen.)

Clinical data included NDA 21-740

Cardiome has submitted information (Table 1) on the efficacy and safety of oxypurinol from three main databases:

- An open-label (OL) retrospective analysis from 533 patients enrolled in the original Compassionate Use Program (CUP); this program is ongoing.
- A prospectively designed 14-week OL study (OXPL-213) involving 79 patients with an extension (A4) that is also ongoing.
- A pharmacokinetic (PK) study (AAI-US-175).

Table 1. Clinical data included in the NDA

Study name	Design	N	% M/F	Age range (mean)	Dose (mg/d)
CUP	OL, dose escalation, ongoing	533	64/36	4-94 (59.8)	100-800
OXPL-213[1]	OL, dose escalation, 14 week	79	52/48	27-83 (61.4)	100-800
A4	OL, 14-week extension	37	71/29	18-39 26.1	300-800
AAI-US- 175	OL, PK	42			300-800

1. The 14-week extension to study OXPL-213 is designated A4 in this review.

Compassionate Use Program

Cardiome has conducted several analyses from the CUP database. However, several features of this program as listed below render this database inadequate for assessing the efficacy or safety of oxypurinol in allopurinol intolerant patients:

- The protocol for compassionate use was not originally designed to formally evaluate the safety or efficacy or oxypurinol. It was open-label, uncontrolled with flexible follow-up visits. Laboratory measurements were not collected systematically. The data analysis plan for this program was not written until October, 2003.
- There is inadequate documentation of allopurinol intolerance before entry.
- There is inadequate documentation of clinical response to therapy
- Baseline data are missing in a substantial number of patients:
  - SUA levels missing in 172 patients (32%)
  - Age and ethnicity are missing in 41% and 31% of patients, respectively
- Post-baseline SUA levels are missing in 127 (24%) of patients.
- The final dose level was not document in 126 (24%) of patients. For analyses, they were assigned a dose category of 300 mg.
- There were 148 patients (28%) that were lost to follow up.

OXPL-213 and extension (A4)

Design/patients:
Open-label, 14-week, uncontrolled study of oxypurinol in 79 patients with symptomatic gout with mild to moderate intolerance to allopurinol. The study has an ongoing extension (A4).

Treatment:
Fixed, dose-escalation, starting with oxypurinol 100 mg/day for the first week, 200 mg/day for the second week, and 300 mg/day up to week 6. At this point, patients who had achieved 2 mg/dL change in SUA would continue on 300 mg/day. Those who did not, would increase to 400, and then 500 mg/day until week 9. Patients who did not achieve the targeted change, would increase up to 800 mg/day by week 10. Completers were offered to continue into the extension (at the same final dose that they were in the base study).

Primary Objectives:
1) To demonstrate the efficacy of oxypurinol in lowering serum uric acid by at least 2 mg/dL after 14 weeks of its administration to symptomatic, hyperuricemic patients who previously developed an intolerance to allopurinol.
2) To describe the toxicity profile of oxypurinol.

Eligibility:
1) **Inclusion**: male and female, =18 years of age, with symptomatic gout and documented intolerance to allopurinol. Laboratories: Hgb > 10 g/dL, WBC > 3.5x 10^9/L, platelets > 100x 10^9/L, ANC > 2.0x 10^9/L; creatinine < 2.0 mg/dL, ALT < 3x ULN (upper limit of normal), AST < 3x ULN, Alk Phos < 5 x ULN, conjugated bilirubin < 1.5 x ULN

2) **Exclusion**: Patients with history of severe allopurinol cutaneous reactions such as Stevens-Johnson (SJS) and Toxic Epidermal Necrolysis (TEN), or severe hepatic or renal reactions such as hepatic necrosis and renal failure, allopurinol hypersensitivity syndrome and those with any > grade 2 hematologic intolerance. Pregnancy. Prior use of oxypurinol. Patients currently receiving thiazide diuretics or uricosurics. Patients were allowed colchicine, NSAIDs, corticosteroids and acetaminophen.

Outcome measures:
Efficacy: Serum uric acid (SUA) levels as a surrogate endpoint for efficacy measured at entry, 6 weeks, 9 weeks (only for those who had not achieved 2 mg/dL at 6 weeks) and at the end of study (weeks 12, 13 and 14).
Safety: Clinical and laboratory evaluations at baseline, 6 weeks and end of study. Patients might be discontinued from the study because of : skin rash, > grade 2 hematologic toxicity, creatinine >2x ULN, AST/ALT >5x ULN, alkaline phosphatase >10x ULN. Patient request.

Primary efficacy analysis:
Change in mean SUA level from baseline (three baseline levels approximately 1 week apart) to the end of study (weeks 12, 13 and 14) in the Intent to Treat (ITT) population. The study would be declared successful if it showed at least a 2 mg/dL change from baseline (including lower bound of the 95% CI) in the ITT population.

Extensive negotiations took place between the Sponsor and the DAAODP regarding this study. Considerations included:

1. This product could potentially fulfill an unmet medical need.
2. Investigators were reluctant to use an allopurinol comparator arm.
3. If successful in demonstrating a reduction in at least 2 mg/dl in SUA and a safety profile that suggested that oxypurinol was safer than allopurinol, the sponsor would carry out a phase 4 study for evaluation of clinically meaningful endpoints (See Appendix 1). This was the rationale for a subpart H submission.

Study Results:
Baseline demographics are presented in Table 1. Most patients also had concomitant medical conditions such as hypertension and hypercholesterolemia and were taking multiple concomitant medications. Of note, 44 % of patients were on prophylactic colchicine. Prior allopurinol intolerance in patients who entered OXPL-213 is presented in Table 2.

Table 2. Prior history of allopurinol intolerance among patients in OXPL-213.

Event Category	N	Adverse Reactions
Cutaneous (involved 63 patients)	24	Erythroderma with or without pruritus or other associated symptoms
	17	Maculopapular or morbilliform rash without desquamation and not associated with clinical symptoms
	11	Maculopapular or morbilliform rash with localized desquamation, covering <50% body surface area (BSA).
	5	Maculopapular or morbilliform rash with localized desquamation, covering >50% BSA.
	7	Exfoliative, eczematoid or vesicular/bullous rash covering <50% BSA.
	1	Urticarial rash with pruritus and covering <50% of BSA requiring PO or topical treatment or IV medications or steroids for < 24 hours.
	5	Urticarial rash with pruritus and covering > 50% of BSA requiring PO or topical treatment or IV medications or steroids for more than 24 hours.
Liver	7	ALT/AST or ALT up to 5x ULN (four patients also had prior skin reactions)
Renal	4	BUN up to 3x ULN and or Creatinine up to 3x ULN (two patients also had prior skin react)
Malaise	6	Including asthenia, fatigue, lethargy – moderate causing difficulty performing some activities (three patients also had prior skin reactions)
Fever	1	Fever in the absence of neutropenia & temperature >40 C for <24 Hours. (this patient also had prior skin reaction)
Mixed	1	BUN up to 3x ULN and or Creatinine up to 3x ULN; ALT/AST or ALT up to 2.5 x ULN and malaise.

As seen in Table 2, 80% (63/79) of patients had prior mild to moderate cutaneous reactions to allopurinol, while an additional 24% of patients had other reactions (alone or in association with cutaneous reactions). The non-cutaneous reactions (liver, renal, malaise and isolated fever), were relatively mild. No patient with prior hematologic reaction to allopurinol was included in the study. Although most patients had a single

episode of allopurinol intolerance, a few had more than one type of skin reactions or cutaneous and non-cutaneous reactions.

Patient disposition: The study enrolled 79 patients. Of those enrolled, 54 completed the study. As per review of case report tabulations and case report forms, it appears that 24 patients discontinued due to adverse events and one due to a protocol violation.

Efficacy results:
A comparison of the analyses of the 14-week base study (OXPL-213) conducted by the sponsor and FDA are presented below in Table 3. As can be seen, two patients were excluded from the ITT analysis conducted by the sponsor, but were included in the analysis conducted by FDA; both analyses imputed missing data with the last observation carried forward (LOCF).

Table 3. Changes from baseline in SUA levels in patients taking oxypurinol.

	(N)	SUA Mean decrease from baseline[1]	95% CI
Sponsor			
ITT	77	1.90	1.61, 2.18
Completers	54	2.32	2.07, 2.57
FDA			
ITT	79	1.78	1.47, 2.08
Patients who achieved SUA of:			
=6 mg/dL	N (%)		
ITT	10 (13)		
Completers	9 (17)		
= 5 mg/dL			
ITT	2 (3)		
Completers	2 (4)		

1. The Sponsor's reported p-values (0.0001) test the hypothesis of mean reduction of zero, that is, the study rejects the hypothesis that oxypurinol reduces SUA levels by zero. The issue is whether this statistically significant change is clinically meaningful. In this case the confidence interval is more informative than the p value.

Analyses of gout attacks during the OXPL-213 and extension study A4:
Fourteen patients (18%) had gout flares during these combined studies as follows:

- Seven had flares during OXPL-213
- Six had flares during the extension study (A4)
- One had flares during both the base and extension phase.

All of these patients experienced a decrease in SUA during the study; two achieved levels = 6 mg/dL. None of these patients discontinued from the study due to their gouty flares. This was undoubtedly influenced by the fact that they were treated with local or systemic corticosteroids and/or NSAIDs or colchicine as needed. Additionally, three patients (with no gouty attacks) had tophi complications such as draining, pain and infection (two patients during the base study and one during the extension study). Characteristics of the patients with gout attacks during the base portion are presented in Table 4.

Table 4. Patients with gout flares during OXPL-213[1]

Age/ gender	*Baseline UA level*	*Final UA level*	*Taking colchicine*	*Day of Flare*	*Oxy dose (mg/d)*
29 M	*9.3- 9- 10.3*	*8.1- 7.9- 8.1*	*Y*	*39*	*300*
48 M	*10.8- 11.9- 11.5*	*9.6-10.5- 9.2*	*Y*	*14-21*	*300*
49 M	*10.7- 12.4- 10.6*	*9.6-10.5- 8.0*	*Y*	*42-90*[2]	*300*
60 M	*10.1- 10.2- 9.6*	*6.4- 6.6- 6.0*	*N*	*26-56*[2]	*300*
77 F	*8- 8.5- 8.6*	*6.2- 5.9- 6*	*N*	*26-27*	*300*
77 F	*9.3- 9.6- 9.6*	*7.6- 8.1- 7.1*	*N*	*7-23*[3]	*200*
				68-73	*300*
68 F	*11.3- 10.3- 11*	*7.3- 8.7- 8.2*	*Y*	*15*	*200*
59 F	*8.0- 8.4- 8.5*	*3.6- 4.8- 4.7*	*N*	*26-31*	*300*

1. No patients were described in CRF as having tophi. Analyses from the extension study are pending.
2. Intermittent flares throughout the study.
3. Had two separate episodes.

While gout attacks are known to occur at the beginning of UA lowering treatment (supposedly because of rapid changes in SUA levels), the exact incidence of this event is unknown. As per a published retrospective review of 354 patients with gout treated with either allopurinol or uricosuric agents, 15% of patients on allopurinol and 8% of patients treated with probenecid had gout attacks within the first 3 months of treatment [Grahame and Scott, 1970]. In another article, 10-24% of patients with gout are reported to have gout flares within the first year of treatment with allopurinol or uricosuric agents [Fam, 1995]

The lack of a placebo-control arm in OXPL-213 makes these finding difficult to interpret whether were related to the flares the oxypurinol therapy or ongoing disease. CRFs for this study did not mention the frequency of gout attacks before study entry.

While it makes intuitive sense that reduction of SUA levels will lead to reduction of gout attacks, a reduction of SUA of only 2 mg/dl may be insufficient to decrease the number of gout flares long-term in patients. By the most favorable analysis in this study (Completers at the end of 14-week study) mean serum UA levels among 54 completers

went from **9.94** (±1.20) to **7.53** (±1.49) mg/dL, a level that is still above the normal range and above the desired 6 m/dL level. Only 9 patients achieved SUA = 6 mg/dL (Table 3).

Safety

Deaths:

There was one death during study OXPL-213 and four during the extension phase (Table 5). Deaths did not appear to be related to oxypurinol. Additional data for patient 005.003 are pending.

Table 5. OXPL-213 and extension A4 - Deaths

14-week base study
Pancreatic carcinoma
Extension study
-Died of end stage liver disease by the time of, before, visit 1 of the extension. Pt had mild LFT elevation during base study. -Anemia, cellulitis, sepsis sepsis after hip surgery, aspiration pneumonia (visit 4) -GI bleed, worsening COPD, (during base study had CHF and MI[2]) -Listed as Multi-organ failure (visit 2). CRF consistent with sudden death

Serious adverse events:

Non-fatal serious adverse events (SAE) during the OXPL-213 and the extension study A4 are presented in Table 6 and 7, respectively.

Table 6. Serious adverse events in study OXPL-213

SAE description
-Rectal hemorrhage -Prostate cancer -Cellulitis, anaphylactoid drug reaction to ciprofloxacin. -Cholelithiasis, cholecystectomy -Lumbar spondylosis. Elective laminectomy. -Myocardial infarction (at 2 ½ months) -Myocardial infarction (day 14). Acute renal failure (day 44).

Table 7. Serious adverse events in extension study A4

SAE description
-Left knee arthroplasty
-Hypertensive emergency
-Cellulitis of left foot
-Renal failure/diverticulitis
-Unstable angina
-Myocardial infarction
-Prostatic cancer, DVT, pneumothorax
-Ventral hernia repair; wound dehiscence
-Right foot infection (after removal of tophi)
-Vertigo
-Thyroid carcinoma
-Back pain, sinusitis, UTI, vomiting
-Breast carcinoma
-Diarrhea, left knee staph infection, URI
-Abdominal pain

Most of the serious adverse events appear unrelated to study drug. Of note, there were three MIs in the base study and one MI and one unstable angina during the extension study. It is likely these cardiovascular are not drug related but reflect associated co-morbid conditions such as hypertension, diabetes, obesity and hypercholesterolemia. The lack of a placebo arm precludes more definitive conclusions relating to the safety of oxypurinol.

Discontinuations due to adverse events

There were 23 patients that discontinued the 14-week base study due to non-fatal adverse events; these are presented in Table 8.

Table 8. Discontinuations due to Adverse Events in study OXPL-213

Event	Prior allopurinol intolerance	Description of oxypurinol intolerance	Approximate day of onset

Skin reaction			
1.	Skin	Erythematous rash	Day 3
2.	"	" "	Day 5
3.	" + Malaise	Maculopapular rash arms/chest/back	Day2
4.	"	Erythematous rash	Day 2
5.	"	""	Day 3
6.	"	Diffuse erythema/ facial swelling	Day 4
7.	"	Diffuse erythema/ pruritus	Day 2
8.	"	Diffuse acneiform rash/gastroenteritis	Day 23
9.	" +Renal	Macular erythematous	Day 2
10.	"	Erythematous-itchy	Day 6
11.	"	Maculopapular, itchy	Day 6
12.	"	Urticarial/macular/bullous rash	First dose
13.	"	Follicular diffuse rash	1 month
14.	"	Erythematous, macular,pruritic rash	Day 3
15.	"	Petechial rash-legs	Day 9
16.	"	Pruritus, Erythematous rash	Day 2
Thrombocytopenia			
17.	Skin	Thrombocytopenia	Day 20
Liver reaction			
18.	Skin/Liver	?ALT/ AST/ AlkPhosphatase	Day 12
Miscellaneous			
19.	Skin/Liver	Fever, chills, polyarthralgia, "viral syndrome" Early term as per medical monitor decision [1]	3 days
20.	Skin	?ALT/ AST/ BUN. Listed as discontinued due to protocol violation, non-compliance. Hx of preexisting Hepatitis C. [1]	Day 54
21.	Malaise Liver/Renal	Listed as discontinued due to nausea/malaise [1]	First dose
22.	Skin	Hypersensitivity to oxypurinol (NOS)	First dose
23.	"	HA, chills, allergic rhinitis	2 months

1. Information to the IND suggests these patients had hepatic intolerance.

The hypersensitivity reactions attributed to oxypurinol were very similar to those previously attributed to allopurinol. Most were cutaneous reaction in patients with prior history of cutaneous intolerance (n=18) and most occurred early in the trial (16 cases within the first week, including three cases after the first dose).

Review of case report tabulations and case report forms suggests that hepatic intolerance was developed by more than one patient. As per Table 8, in addition to the patient reported by the sponsor as having hepatic intolerance, three patients who discontinued from the study may have had hepatic intolerance. Additionally, two patients had mild transaminase elevation and completed the study OXPL-213 but did not continue into the extension. One of these was a patient who had had mild LFT elevation at baseline and throughout the base study, and was reported to have died of "end stage liver disease" before entering the extension study. Additional information on this patient is pending. Therefore, there could be six liver reactions among 79 patients who received oxypurinol. Although the case report forms are not very helpful in determining causality, four of the six occurred in patients with a prior history of liver intolerance to allopurinol. Eosinophil counts were not consistently obtained in these patients. Those patients who had available eosinophil counts did not show increase in eosinophil levels.

One patient with prior history of cutaneous intolerance developed thrombocytopenia.

Four patients discontinued during the extension study A4; they are listed in Table 9. Overall, the patient disposition for the extension study is unclear at the time of preparation of this background document. The sponsor states that 48 patients entered the extension study, however, case report tabulations include data for 37 patients only.

Table 9: Discontinuations due to adverse events in A4 extension study

- Rash arms/legs/trunk
- Adverse event related to oxypurinol (rash versus MI)
- Right foot infection (after surgical procedure to remove tophi)
- Left foot surgery, hematuria

Two of these discontinuations appear related to oxypurinol therapy. This table does not include patients who had abnormal laboratories at the end of the base study and therefore did not continue into the extension. Additionally, three patients refused further treatment, one was lost to follow-up and for one the reason is unclear.

Adverse events among patients with documented allopurinol re-challenge or desensitization in study OXPL-213:

According the Sponsor, there were 26 patients with documented re-challenge or desensitization of allopurinol. Among the patients, the following adverse events occurred:

- 1/26 died of pancreatic carcinoma at week 6
- 7/26 developed intolerance to oxypurinol (same as to allopurinol: 5 skin; 1 liver;1 malaise)
- 18/26 completed 14 weeks of treatment. One of them had a mild skin rash and did not enter the extension study. The other 17 entered the extension study A4.

Therefore, 18 of 26 patients (69%) who had failed documented allopurinol re-challenge or desensitization were able to tolerate oxypurinol without further allergic reactions for up to 14 weeks. However, the cause of discontinuation is unclear for three patients. Additionally, it is unclear whether three other patients actually entered the extension study or not. Additional information is pending at the time of this review.

AAI-US- 175 (Pharmacokinetic study):

Oxypurinol has non-linear pharmacokinetics. The dose of oxypurinol can not be easily correlated with that of allopurinol. The following summarizes oxypurinol PK characteristics:

- Oral administration of single-doses of 100 and 800 mg doses increases systemic exposure only about 2-fold.
- A high-fat meal increases systemic availability about 2-fold.
- Relative bioavailability of oxypurinol is about 30% of that from allopurinol. Based on oxypurinol exposure, equivalent allopurinol doses from oxypurinol doses of 100, 300, 600 and 800 mg are approximately 58, 78, 81, and 112 mg, respectively.

SUMMARY

1) Oxypurinol treatment is associated with a modest reduction in SUA levels in 79 patients with hyperuricemia after 14 weeks of treatment (mean change 1.7 mg/dL, 1.47, 2.08 95% CI in the ITT population).

2) Oxyprim™ appears to provide a subtherapeutic lowering of SUA for the majority of symptomatic hyperuricemic patients.

3) Fourteen patients experienced gouty flares and three other patients had tophi complications during OXPL-213 and its extension. The lack of a placebo control or an allopurinol comparator arm hampers an adequate interpretation of these findings.

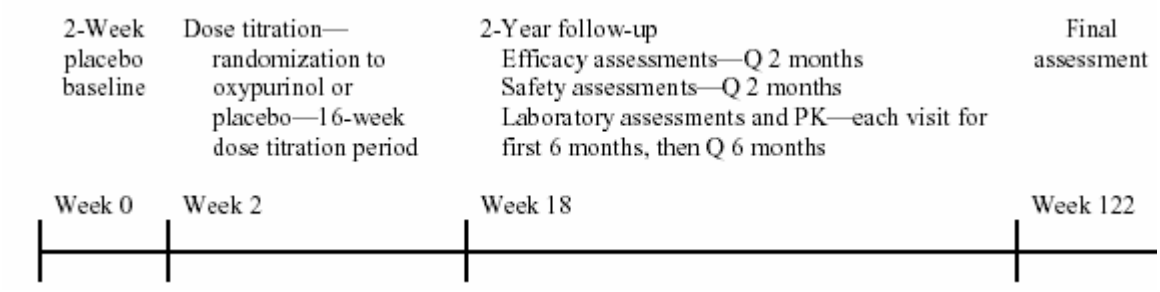
4) In OXPL-213, up to one third of the patients developed intolerance to oxypurinol. Most patients developed the same kind of reaction that they had experienced with allopurinol; the majority were skin reactions and occurred early in treatment. However, six patients developed LFT elevation (four of them had a prior hepatic reaction to allopurinol) and there was one patient who developed thrombocytopenia.

Appendix 1

Proposal for a Phase 4 Oxypurinol Study (modified from sponsor)

1. Design/patients: Multi-center, double-blind, randomized, placebo controlled, two-year study in 240 patients with symptomatic gout, with documented allopurinol intolerance and at least 6 gout attacks in the year before enrollment.

2. Treatment: dose titration: 100 mg/day x 2 weeks, dose gradually escalated by 100 mg/day every 2 weeks, if indicated, to achieve a SUA of <6 mg/dL (supervised by a blinded 3rd party physician based on adverse events and laboratory data) up to a maximum daily dose of 800 mg.



Oxypurinol 100 mg---800 mg
Or Placebo
(2:1 randomization)

3. Objective: Primary: To evaluate efficacy and safety of oxypurinol therapy, over at least a 2-year period, in reducing the number of acute attacks.

Secondary: Reducing SUA from baseline
SUA <6mg/dL
Size and number of swollen joints
Size and number of tophi
Decreasing hospital admissions for gout
Emergency visits for gout flares
Frequency of symptomatic nephrolithiasis
Reducing use of anti-inflammatory and other rescue medications
Improving overall quality of life (SF-36)

4. Eligibility: Inclusion: M or F, 18 to 80 years. Mild to moderate skin or other allergic reactions to allopurinol with recurrence of symptoms on re-exposure to allopurinol, on a stable treatment for gout for at least 3 weeks prior to study entry.

Exclusion: patients with severe or serious adverse events related to allopurinol. Pregnancy or lactation.

Concomitant medications. Permitted:
Analgesics, NSAIDS, colchicine, steroids and uricosuric agents. Low dose aspirin if benefits are believed to outweigh the risk of increasing SUA. Ethanol consumption should be discouraged.

Concomitant medications. Prohibited: Ampicillin and related semi-synthetic penicillins; thiazide and loop diuretics because they can reduce renal uric acid excretion and increase SUA.

5. Safety outcomes: History and physical, vital signs, documentation of adverse reactions and SUA levels at baseline, every two weeks until week 18, then every two months until final assessment at 30 months. Laboratories: Hematology, renal function and liver function tests at baseline, at weeks 4 and every two weeks until week 18, then every six months until month 30.

6. Statistical Considerations and statistical plan

6.1 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint will be the number of documented acute gout attacks, requiring additional treatment and reported by the patient to the investigator, during the 2-year study period.

Secondary Efficacy Endpoints

- Reduction in SUA
- 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
- SF-36 Quality-of-Life Questionnaire

6.2 Safety Endpoints

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

7. Statistical and analytical methods.

The primary efficacy analysis will consist of a comparison between the mean number of documented 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.