The Effectiveness of Newly FDA Approved Uloric (Febuxostat) Versus the Conventionally Used Zylolprim (Allopurinol) in Treatment of Hyperuricemia and Chronic Gout in the Adult Population

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Abstract
Background: Gout is a metabolic syndrome characterized by: 1.) hyperuricemia and deposition of urate (uric acid) crystals causing attacks of acute inflammatory arthritis; 2.) tophi around the joints and possible joint destruction; 3.) renal glomerular, tubular and interstitial disease and; 4.) uric acid urolithiasis. According to the U.S. Census Bureau, whose numbers were obtained from a year 2005 population estimate study, gout affected an estimated 6.1 million adults aged 20 years old and older. Many challenges are faced with the treatment of gout, however, the mainstay of hypouricemic treatment has been the conventional use of allopurinol. In February of 2009, the FDA approved a new medication, Uloric (febuxostat), which claimed to be more effective than Zylporim (allopurinol) for chronic sufferers of gout who have long been dissatisfied with previously available options in the treatment of hyperuricemia.

Hypothesis: Patients who did not receive the expected level of benefit from treatment with allopurinol to adequately reduce urate levels in the body, now have a greater likelihood of success with the aid of a new pharmaceutical tool, febuxostat.

Study Design: A review of literature on Uloric (febuxostat), as well as Zyloprim (allopurinol), was performed via an exhaustive search of available studies within the time frame ranging from 2004 through the present, completed on the adult population, utilizing Medline-Ovid, Web of Science, WorldCat.org, PubMed, and the Chochrane Central Register of Randomised Controlled Trials.

Methods: Including a search of the keywords listed below, multiple reference lists of articles obtained were also checked for any additional sources that might have been overlooked in the original search. Studies that were included were phase I through phase III clinical trials that examined solely febuxostat, as well as febuxostat compared to allopurinol. Studies that were excluded were those that did not primarily focus on the treatment of gout utilizing the two aforementioned medications—e.g. probenecid, indomethacin, and colchicine. As a result, a systematic review of the obtained literature regarding the comparison of febuxostat-treatment versus allopurinol-treatment on hyperuricemia and gout was completed.

Results: A combination of phase I and phase II trials, eight in total, were analyzed for background testing completed on the new drug. Two critical Phase III Randomly-Controlled Trial articles with two additional long term studies were obtained that displayed febuxostat to have an advantage over allopurinol in the treatment of hyperuricemia and gout.

Conclusion: Febuxostat proved to be more effective in reducing the serum uric acid concentration in subjects with hyperuricemia and gout. Febuxostat showed promising hypouricemic effects among those individuals tested with renal-impairment, distancing itself from allopurinol. However, due to the recentness of FDA approval and unfamiliarity in the clinic setting, further observations of febuxostat’s long term efficacy and safety need to be done on a greater number of gout and hyperuricemic patients.

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THE EFFECTIVENESS OF NEWLY FDA APPROVED ULORIC
(FEBUXOSTAT) VERSUS THE CONVENTIONALLY USED ZYLOPRIM
(ALLOPURINOL) IN TREATMENT OF HYPERURICEMIA AND CHRONIC
GOUT IN THE ADULT POPULATION

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Biography

Kyle K. Ohisa was born and raised in Honolulu, Hawaii, but completed his undergraduate studies in Northern California at the University of California at Davis. At UCD, he majored in Japanese with a strong minor in the Biological Sciences. After completion of his undergraduate degree, he returned home to continue his pursuit of learning Medicine through additional Science classes and employment in various medical specialties as an assistant. Also, his involvement with the Honolulu Heart Program – Autopsy Team (“A-TEAM”), affiliated with the Kuakini Medical Center, fueled his experience in research, and enabled great professional growth. Pacific University nurtured his growth further by means of a rigorous Physician Assistant Studies Program, which he will proudly (PROUDLY!) complete in October of 2009.
Abstract

**Background:** Gout is a metabolic syndrome characterized by: 1.) hyperuricemia and deposition of urate (uric acid) crystals causing attacks of acute inflammatory arthritis; 2.) tophi around the joints and possible joint destruction; 3.) renal glomerular, tubular and interstitial disease and; 4.) uric acid urolithiasis. According to the U.S. Census Bureau, whose numbers were obtained from a year 2005 population estimate study, gout affected an estimated 6.1 million adults aged 20 years old and older. Many challenges are faced with the treatment of gout, however, the mainstay of hypouricemic treatment has been the conventional use of allopurinol. In February of 2009, the FDA approved a new medication, Uloric (febuxostat), which claimed to be more effective than Zylporim (allopurinol) for chronic sufferers of gout who have long been dissatisfied with previously available options in the treatment of hyperuricemia.

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**Conclusion:** Febuxostat proved to be more effective in reducing the serum uric acid concentration in subjects with hyperuricemia and gout. Febuxostat showed promising hypouricemic effects among those individuals tested with renal-impairment, distancing itself from allopurinol. However, due to the recentness of FDA approval and unfamiliarity in the clinic setting, further observations of febuxostat’s long term efficacy and safety need to be done on a greater number of gout and hyperuricemic patients.

**Keywords:** Gout, Uloric, Febuxostat, TMX-67, Treatment, Allopurinol, Zyloprim, Xanthine Oxidase Inhibitors, Hyperuricemia, Uric Acid.
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To my Kazoku and tomodachi, the love and support throughout every year of my education has been joys and struggles which we have endured together. Nothing would be possible without your love and encouragement. It is in my hopes that I can represent my family with honor and compassion to make my mark in this world. We made it. Thank you. I love you.
# Table of Contents

Biography.................................................................................................................. 2  
Abstract..................................................................................................................... 3  
Acknowledgements................................................................................................... 4  
Table of Contents.................................................................................................... 5  
List of Tables........................................................................................................... 6  
List of Figures.......................................................................................................... 6  
List of Abbreviations............................................................................................... 6  
Introduction............................................................................................................. 7  
Background............................................................................................................. 8  
Purpose of Study..................................................................................................... 11  
Methods and Materials......................................................................................... 13  
Results.................................................................................................................... 13  
Discussion / Analysis............................................................................................. 21  
Conclusion / Recommendations........................................................................... 24  
Figures..................................................................................................................... 25  
Tables...................................................................................................................... 26  
References.............................................................................................................. 39  
Final Page (End) .................................................................................................... 42
**List of Tables**

Table I: Studies conducted to assess solely Febuxostat (Preapproval of FDA)

Table II: Trials comparing febuxostat versus allopurinol including long-term trials of febuxostat usage.

Table III: Comparison of outcomes from Clinical Trials FACT, APEX, and FOCUS

**List of Figures**

Figure I: The development of gout in terms of sources and excretion of uric acid

Figure II: Simplified pathway of uric acid metabolism with mechanisms of discussed gout medications

**List of Abbreviations**

APEX..........................Allopurinol-and Placebo-Controlled, Efficacy Study of Febuxostat

FACT..................................Febuxostat versus Allopurinol Controlled Trial

FDA.................................................U.S. Food and Drug Administration

NSAID...........................................Non-Steroidal Anti-Inflammatory Drug
THE EFFECTIVENESS OF NEWLY FDA APPROVED ULORIC (FEBUXOSTAT)
VERSUS THE CONVENTIONALLY USED ZYLOPRIM (ALLOPURINOL) IN
TREATMENT OF HYPERURICEMIA AND CHRONIC GOUT IN THE ADULT
POPULATION

Introduction

In February of 2009, the FDA approved a new medication, Uloric (febuxostat), which claimed to be more effective than Zylporim (allopurinol) for chronic sufferers of gout who have long been dissatisfied with previously available options in the treatment of hyperuricemia. A comparison between febuxostat and allopurinol proved necessary to aid in the treatment of multiple individuals that questioned the efficacy and necessity to treat gout conventionally with the medication allopurinol. Chronic sufferers of painfully intense gout attacks, these individuals were in search of an alternative to failed multiple attempts solely treated with allopurinol. Since clinical profiles were quite similar in presentation, the patients lacked any other comorbidities with comparable medical histories, treatment with the newly FDA-approved medication, Uloric (febuxostat), was initiated.

Prior to the start of drug administration, however, lab values needed to be drawn to assess the serum uric acid level, liver function, renal function, and overall assessment of health (lipid panel, complete blood count, comprehensive metabolic profile, and urinalysis). Focusing on the uric acid (urate) levels found in the individuals, all displayed a level of >8.0mg/dL, diagnostically implicating hyperuricemia (Normal range= 3.0 mg/dL and 7.0 mg/dL). All other lab values were within normal limits, so the drug prescriptions were written and obtained. Future follow up appointments were scheduled for close monitoring. As a result, within 2 weeks, the subjects’ uric acid levels had been
reduced nearly 40% to <6.0 mg/dL with no acute gout attacks experienced within the short treatment time prior to follow up.

As a Physician Assistant student, inquiring the proper methods to treat certain ailments and illnesses was thought to be a task with which the information at goal would be found with conclusive, concrete certainty. However, the realistic roots of Clinical Medicine and Evidence Based Medicine would reveal the aforementioned ideology to be naïve in nature. The destination, or endpoint, is not necessarily the most difficult attribute of Medicine, as ultimately, the goal is to heal, it is the process or path through which we reach that goal which proves to be the most complex. With that being stated, “Is Uloric (febuxostat) a clinically wiser choice over Zyloprim (allopurinol) for treatment of hyperuricemia which is found in gout?”

**Background**

Gout is a metabolic syndrome characterized by: 1.) hyperuricemia and deposition of urate (uric acid) crystals causing attacks of acute inflammatory arthritis; 2.) tophi around the joints and possible joint destruction; 3.) renal glomerular, tubular and interstitial disease and; 4.) uric acid urolithiasis. However, all of the above do not have to be concomitantly present to clinically establish an individual with gout. The disease most commonly affects monoarticularly, the first toe (podagra), foot, ankle, knee, fingers, wrist and elbow, but can affect any joint.²

There exist four classifications, or stages, of gout that are distinguished, with the first noted as Asymptomatic Hyperuricemia. Elevated levels of urate are present within the body, but the individual does not display symptoms clinically. It is common for a
patient to have an elevated uric acid level for a length of time, possibly even for years, before an acute attack may occur. While in this stage, it is not necessary to administer treatment, including any uric acid-lowering agents.

Stage 2, an acute gout attack or flare, comprises of the build up and small deposits of monosodium urate crystals in and around specific joint spaces. The invasion and buildup within the joint spaces triggers a cascade of physiologic events that leads to the inflammation of the affected joint(s). Characteristically, the patient may suffer pain, redness, swelling, and warmth, which may last for lengths of time ranging from days to weeks. Within the acute gout flare, it is primarily the arthritis that is treated, with the underlying hyperuricemia weeks later, as an aggressive and sudden reduction of serum uric acid often precipitates further episodes of gouty arthritis. Therefore, NSAIDs are the treatment of choice for acute gout flares. Traditional use of the medication Indomethacin has been the NSAID of choice, but this should not preclude the use of alternative drugs from the same class. Other drugs including Colchicine and corticosteroids (useful in patients with contraindications to the use of NSAIDs) have also been utilized by clinicians in the treatment of acute flares.

Intercritical Gout occurs in a patient who has had prior gout flares, which have successfully subsided and who has no current expression of gout symptoms. A patient may report normal joint function, though hyperuricemia continues to occur with an increasingly greater possibility for damage in tissues due to continued deposition of urate crystals. As an indication of the progression and severity of gout, the intercritical periods between flares will shorten as the disease escalates. It is at this phase, which may include frequent acute arthritis flares, tophaceous deposits, and/or renal damage, that
serum uric acid reduction intervention is indicated. For introductory purposes, two classes of agents may be used to reduce uric acid: uricosuric drugs—e.g. probenecid or sulfipyrazone; and allopurinol, a xanthine oxidase inhibitor.

The final stage of progression, Chronic Gout, is typified by a resulting destructive and disabling inflammatory process causing ongoing pain and aching of the joint(s). Chronic tophaceous arthritis is a product of the continuous deposition of urate crystals around and within the joint space. In multiple cases, deformities and destruction of the bone and joints involved have occurred, not surprisingly, causing a reduction in quality of life due to the damage and pain.

Clinical manifestations of acute and chronic arthritis, tophi at the joints, and renal disease, are direct representations of the length and intensity of hyperuricemia in individuals that suffer from gout. Uric acid, therefore, is the fulcrum on which clinicians base gout-treatment and potential resolution due to its direct association with the risk of gout.4,5 Consequently, the logical, most advantageous treatment methodology, entails maintenance control of serum uric acid levels below the supersaturation concentration threshold within the human body. By doing so, urate crystal deposition into the certain anatomical locations is fundamentally avoided. Monosodium urate crystals tend to supersaturate and precipitate into body fluids and the human body’s blood serum, if the concentration is >6.8mg/dL. In effect, the target of urate-lowering therapy is to reduce patients’ serum urate concentrations ideally to <6.0mg/dL in order to cut the number of gout attacks, or better yet, to prevent any possibility of a recurrent gout attack.6

The amount of urate in the body depends on the balance between dietary intake, the synthesis, and rate of excretion within each individual. Gout patients fall into two
groups, which sometimes overlap. In the first group, which accounts for roughly 10% of cases, hyperuricemia results from urate overproduction. Found in the second group, the other 90% of cases, hyperuricemia results from underexcretion of urate from the body.\(^7\)

Figure 1 displays a brief, overall physiological schematic of urate balance within the human body. As a catabolic product of purine metabolism, uric acid can reach hyperuricemic levels that can potentiate the risk of causing gout symptoms. Uric acid is formed when hypoxanthine, the precursor of xanthine in the metabolic process of purine to urate, is enzymatically degraded by the liver enzyme, xanthine oxidase. Xanthine oxidase also catalyzes the final step of the metabolic pathway, with the conversion of xanthine to urate (see Figure 2). Most excretion of excess urate is then handled by the kidneys, while a third is done by the gastrointestinal tract. It is through these simplified mechanisms where uricosuric drugs, allopurinol, and febuxostat, take action chemically.

Uricosuric drugs such as probenecid or sulfinpyrazone block the tubular reabsorption of the filtered urate thereby reducing the excess urate within the body fluids. Obviously, due to their mechanism and effect on the kidneys, the uricosuric agents are counterindicated for patients with renal insufficiency or who have renal impairment. Allopurinol is a xanthine oxidase inhibitor which acts on the catabolic pathway from hypoxanthine to urate. Febuxostat acts in very much the same manner as allopurinol, however, unlike the latter, febuxostat is not purine-like in structure, nor does it affect any other enzymes in the purine and pyrimidine pathways.\(^8,9\)

**Purpose of Study**

According to the U.S. Census Bureau, whose numbers were obtained from a year 2005 population estimate study, gout affected an estimated 6.1 million adults aged 20
years old and older. Gout is also especially common in Pacific Islanders, e.g. Filipinos and Samoans, who are a large representation of the population of Hawaii. Additionally and often overlooked, hospitalized patients frequently suffer acute gout attacks due to unavoidable changes in their dietary regimen, fluid intake, and medications. These changes have the potential then, to lead either to rapid reductions or to increases in the serum urate level.

Studies rooted in obtaining evidence to display the upslope of gout prevalence and disease burden prove that the need for care alternatives and techniques is evident. Therapeutically, the interventions and medications currently available fall short of success. On that note, allopurinol can be utilized as a first-line drug for serum urate-lowering therapy, and can be administered in doses up to 800mg daily. However, clinicians are commonly reluctant to prescribe dosages of more than 300mg per day due to the medical risk of possible renal damage associated in higher doses. Consequently, by restricting the dosage so, the drug often fails to adequately treat the underlying hyperuricemia found in gout.

Quality of life and adherence to urate-lowering therapies of the affected patients are directly hindered in parallel to the shortcomings in quality of care administered. With the advent of the newly FDA approved febuxostat, a potential alternative is at the least, now available for utilization. Therefore, it is hypothesized that patients who did not receive the expected level of benefit from treatment with allopurinol to adequately reduce urate levels in the body, now have a greater likelihood of success with the aid of a new pharmaceutical tool, febuxostat.
Methods and Materials

A review of literature on Uloric (febuxostat), as well as Zyloprim (allopurinol), was performed via an exhaustive search of available studies within the time frame ranging from the year of 2004 through the present, completed on the adult population, utilizing Medline-Ovid, Web of Science, WorldCat.org, PubMed, and the Chochrane Central Register of Randomised Controlled Trials. Key search terms included in the search were: “Gout”, “Uloric”, “Febuxostat”, “TMX-67”, “Treatment”, “Allopurinol”, “Zyloprim”, “Xanthine Oxidase Inhibitors”, “Hyperuricemia” and “Uric Acid”. Multiple reference lists of articles obtained were also checked for any additional sources that might have been overlooked in the original search. Studies that were included were phase I through phase III clinical trials that examined solely febuxostat, as well as febuxostat compared to allopurinol. Studies that were excluded were those that did not primarily focus on the treatment of gout utilizing the two aforementioned medications—e.g. probenecid, indomethacin, and colchicine. As a result, a systematic review of the obtained literature regarding the comparison of febuxostat-treatment versus allopurinol-treatment on hyperuricemia and gout was completed.

Results

In regards to obtaining scientific clinically-tested data dealing with febuxostat (Uloric), two critical Phase III Randomly-Controlled Trial articles (The Febuxostat versus Allopurinol Controlled Trial, or FACT; and The Allopurinol-and Placebo-Controlled, Efficacy Study of Febuxostat, or APEX study) were obtained from database searches which specifically compared the recently formulated urate-lowering drug with
allopurinol. Also, a series of relatively long-term studies (FOCUS and EXCEL studies) have been carried out to assess the attributes of febuxostat, as the FACT and APEX studies were stopped after 52 weeks and 28 weeks respectively. Prior to the comparison trials listed above, Phase I and II clinical trials were as well conducted, however more emphasis will be placed onto the controlled trials that directly contrasted febuxostat and allopurinol in the treatment of hyperuricemia and gout.

A succinct summary of Phase I and Phase II clinical tests and publications can be seen on Table I within the Tables section of this review. The table highlights multiple aspects of which febuxostat was reviewed. Khosravan, R. put forth a bulk of the findings including the effects of Age and Gender on febuxostat on healthy individuals (n=96), the effects of food and/or antacid use on febuxostat on healthy individuals (n=92), the effect of combining NSAID (indomethacin and/or naproxen) use with febuxostat on healthy individuals (Study 1: n=26 and Study 2: n=25), the effect on hepatic impairment on febuxostat (n=26), and a dose escalation study (n=12) that contributed to further other dose-studies of febuxostat performed by Mayer and Becker. The outcomes of the Khosravan works were as follows: No dose adjustments of febuxostat based on gender or age alone were necessary\textsuperscript{15}; febuxostat can be administered regardless of food or antacid intake\textsuperscript{16}; febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen necessary\textsuperscript{17}; febuxostat appears to be generally safe and well tolerated in mildly and moderately hepatic groups —no dose adjustments were necessary in subjects with mild to moderate hepatic impairment\textsuperscript{18}; and lastly, the trials derived a linear pharmacokinetic and dose-response relationship for febuxostat dosages within 10-120mg range with a note that febuxostat was found to be
extensively metabolized and renal function did not seem to play an important role in elimination from the body.\textsuperscript{19, 15, 16}

Mayer, M. provided further insight with a Phase I, parallel-group, open-label, multiple-dose exploration (n=31) that studied the safety, pharmacokinetics, and pharmacodynamics of febuxostat in subjects with varying degrees of renal impairment. Febuxostat 80mg was administered once-daily for 7 days, and although a plasma exposure to the drug and its metabolites was higher in subjects with increasing degrees of renal impairment, the percentages of reduction in serum uric acid levels were comparable, regardless of renal function. Therefore, it was concluded that a once-daily 80mg dose of febuxostat appeared to be safe and well tolerated in different renal function groups, requiring no dose adjustments necessary based on differences in renal function in individuals.\textsuperscript{20}

Additional to the dose-escalation study performed by Khosravan, Becker M.A. performed a Phase I, multiple-dose, placebo-controlled, dose-escalation study (published in 2004), as well as a Phase II randomized, multicenter, double-blinded, placebo-controlled, dose-response clinical trial (published in 2005). The former consisted of 154 healthy subjects, female and male (19-54 years old), tested to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of febuxostat over a range of oral doses. It was found that febuxostat effectively decreased serum uric acid concentrations in a dose-linear manner, with once-daily dosing of up to 120mg, and that doses in excess of 120mg daily did not appear to provide significant additional hypouricemic effects. Also important, Becker noted that since febuxostat did not appear to cause significant
reduction in total purine synthesis, he could deduce that the sole mechanism of action of febuxostat was indicated to be a xanthine oxidase inhibitor.21

Within Becker’s Phase II clinical trial, 153 individuals were separated into groups to assess the safety and efficacy of once-daily oral febuxostat in doses of 40mg, 80mg, 120mg, versus placebo for twenty-eight days. The degree of serum uric acid reduction was significantly greater in all febuxostat treatment groups compared to placebo by day seven, and those values were maintained over the 28-day study period. In regards to adverse events, febuxostat and placebo groups were found to be equal in incidence, with few serious adverse events occurring. Renal insufficiency was not assessed in this study, and future studies were indicated (addressed by studies completed by Mayer in 2005 and Khosravan in 2006 discussed above). Data suggested therapeutic dosages of febuxostat were likely to fall in the range of 80mg – 120mg per day, and it provided confirmation that febuxostat’s mechanism of action was xanthine oxidase inhibition.22

Concentrating now on the Febuxostat versus Allopurinol Controlled Trial (FACT), the attention shifts to contrasting the efficacy and safety of febuxostat versus allopurinol in adult subjects with hyperuricemia and gout. The FACT study was a Phase III, randomized, double-blinded, 52-week, multicenter trial that compared adult individuals with gout and a serum uric acid level of at least 8.0 mg/dL. A stated total of 762 subjects were recruited and randomized by a computer-generated randomization schedule into groups that would either receive febuxostat 80mg once-daily, febuxostat 120mg once-daily, or allopurinol 300mg daily for a time period of 52 weeks. For subjects that were already receiving urate-lowering therapy, a washout period of two weeks occurred before randomization. During the two week washout, as well as the first
eight weeks of double-blinded treatment, naproxen (250mg twice a day) or colchicine (0.6mg daily) was administered for gout flare prophylaxis.

Physical examination checkpoints were performed at two weeks and four weeks, and then monthly thereafter. Data from each patient/subject consisted of vital signs, serum urate concentration, renal function, compliance with study drugs, laboratory tests, concomitant medication use, gout flares, and adverse events. The primary efficacy endpoint was serum urate concentration of less than 6.0mg/dL at each of the last three monthly measurements. Secondary efficacy endpoints included the proportion of subjects with serum urate levels of less than 6.0mg/dL at each visit and the percentage reduction from baseline in the serum urate concentration at each visit. Additionally just as important, the clinical endpoints, were the percentage reduction from baseline in tophus area, the change in number of tophi at each visit, and the proportion of subjects requiring treatment for acute gout flares from weeks 9-52.

As seen in Tables 2 and 3, the primary endpoint of reaching a serum urate concentration of <6.0mg/dL at all of the final three measurements at monthly intervals was reached in 53%, 62%, and 21% in the febuxostat 80mg, febuxostat 120mg, and allopurinol 300mg subject groups, respectively. P-values of <0.001 were derived for the comparison of each febuxostat group with the allopurinol group establishing it as a statistically significant finding. The overall outcome in regards to the incidence of acute gout flares displayed a gradual decrease similar across all test groups. By weeks 49-52 (final visit interval), the flare incidences were noted to be 08%, 06%, and 11% in the febuxostat 80mg, febuxostat 120mg, and allopurinol 300mg groups, respectively. Another clinical outcome, the median reduction in tophus area, displayed the values of
83% in patients who received febuxostat 80mg, and 66% reduction in patients of the febuxostat 120mg group. In comparison, the allopurinol 300mg test group only had a median tophus area reduction of 50% (p-value >0.05, again, proving to be of statistical significance). Lastly, a higher number of subjects (n=98) from the febuxostat 120mg group discontinued intervention versus both the febuxostat 80mg (n=88) and allopurinol 300mg (n=66). Despite the most common treatment-related adverse events being abnormal liver-function tests (febuxostat 80mg = 4%, febuxostat 120mg = 5%, and allopurinol 300mg = 4%), diarrhea, headaches, and joint-related symptoms, the authors concluded that the febuxostat arms proved to be more successful and effective than the allopurinol control group at reducing the serum uric acid levels in individuals with gout.23

The Allopurinol-and Placebo-Controlled, Efficacy Study of Febuxostat, or APEX study, aimed to compare the safety and efficacy of orally administered febuxostat with placebo and allopurinol in subjects with hyperuricemia and gout. Also, the study attempted to solidify, confirm, and expand upon the aforementioned FACT trial by assessing the effects of treatment in subjects with impaired renal function (serum creatinin level >1.5 - ≤2.0mg/dL). Very much like the FACT study, the APEX study was a phase III, randomized, double-blinded, allopurinol-and-placebo-controlled, parallel-group trial which was conducted at 167 sites in the US and involved 1,072 subjects for 28-weeks. Inclusion criteria called for participants with gout, hyperuricemia (≥8.0mg/dL sUA), and normal (serum creatinine level ≤1.5mg/dL) or impaired (serum creatinine level >1.5 to ≤2.0mg/dL) renal function at day -2.

After a 2-week washout period for patients with previous urate-lowering therapy, subjects were randomized into a 2:2:1:2:1 ratio of once-daily febuxostat 80mg, febuxostat
120mg, febuxostat 240mg, allopurinol (300mg or 100mg, dependent on renal function), or placebo. Similar to the FACT study, either colchicine 0.6 mg once daily or naproxen 250mg twice daily per oral was provided during the washout period, and was continued for the first 8 weeks of the study as a prophylaxis for gout flares. Physical examination checkpoints were established every 4 weeks for serum urate levels, laboratory assessments, gout flares, adverse events, concomitant medications, and to examine the number and size of palpable tophi.

The primary endpoint of reaching a serum uric acid level of <6.0mg/dL in the final 3 visits was reached by subjects with proportions of 36%, 52%, 66%, 10%, and 0% in the febuxostat 80mg, 120mg, 240mg, allopurinol 300mg, and placebo groups respectively. A p-value of <0.001 was obtained for febuxostat achieving a greater proportion of subjects <6.0mg/dL versus allopurinol or placebo. For the subjects with moderate renal impairment, 44%, 46%, 60%, and 0% achieved a serum uric acid level of <6.0 in the febuxostat 80mg, 120mg, 240mg, and allopurinol 100mg groups respectively.

At the checkpoint of 28 weeks, the proportions of 76%, 87%, 94% 41%, and 1% of the febuxostat 80mg, 120mg, 240mg, allopurinol 300mg, and placebo groups achieved a serum uric acid level of <6.0mg/dL. In this case, a p-value <0.05 was calculated for the comparison of the febuxostat groups versus allopurinol. The overall reduction of serum uric acid showed a 45% decrease for febuxostat 80mg, 52% decrease for febuxostat 120mg, 66% decrease in febuxostat 240mg, 34% decrease for allopurinol 300mg, and a 3% decrease in the placebo group.

In regards to the incidence of gout flares, there proved to be no significant statistical differences between the treatment groups. This result also held for the number
of tophi and median tophus size between all tested groups. Proven to have a greater impact, however, as with the FACT study, the list of adverse events was focused on the outcome of abnormal liver function results

Adverse events, listed by frequency, included, but were not limited to, upper respiratory tract infections, musculoskeletal and connective tissue symptoms, diarrhea, joint-related signs and symptoms, headaches, and abnormal findings on liver function tests. Amongst the febuxostat 80mg group 17/51 (6%), the febuxostat 120mg group 10/51 (4%), the febuxostat 240mg group 06/51 (4%), the allopurinol 300mg group 15/51 (6%), and placebo group 03/51 (2%) were noted with abnormal liver-function results. In fact, 12 withdrew from the study due to abnormal liver function values (see table for number of subjects). As a final note, 78 subjects across the treatment groups lead to the discontinuation of therapy due to adverse events. These results determined that febuxostat demonstrated a greater efficacy compared to allopurinol and placebo in the reduction and the maintenance of the serum uric acid level below the suggested therapeutic value of 6.0mg/dL.24

A long term study termed the FOCUS study followed subjects for 5-years, and has measured results similar to endpoints obtained in the FACT and APEX studies. The number of subjects who had a serum uric acid level <6.0mg/dL throughout the long-term study was 54/58 subjects, or 93% across all febuxostat dosages (40mg, 80mg, 120mg daily). Dealing with resolution of tophus since baseline of the study, 18 of 26 subjects experienced complete resolution. No deaths had taken place, and after one year of stable dosing, all subjects have had less than one gout flare per year (similar to findings of the EXCEL study noted in Table 2). The data led the authors to conclude that long-term
treatment with febuxostat resulted in long-lasting maintenance of serum uric acid levels below 6.0mg/dL, and nearly complete abolition of gout flares and tophi for a majority of subjects within the study.25

Discussion / Analysis

The primary goal of this review was to identify evidence from current available medical literature to weigh the benefits and costs of using a newly FDA-approved drug, Uloric (febuxostat), versus a mainstay, conventional drug, Zyloprim (allopurinol) for the treatment of hyperuricemia and gout. With the research and development of a new drug, many challenges are faced by study facilitators to ensure a scientific, unbiased protocol and implementation. Ideally, one could assume that economic influences and endeavors should not influence the procedure, the methods, nor the outcome of the research. However, realistically, there is always an inkling of skepticism around a study which has been fueled financially by the pharmaceutical company producing the drug, as seen with the studies performed on febuxostat.

Since problems with such studies are being highlighted, the potential lack of objectivity is not the only issue. Both the FACT and the APEX studies claim to be double-blinded, but fail to specify the methods of blinding of the medical personnel. It is unclear from what was presented in the evidence whether the investigators and medical personnel who administered the interventions were blinded to the treatment similar to the subjects. Again, this creates some hesitation to accept the studies due to lack of clarity within methods.

Within the direct comparison of febuxostat with allopurinol, it is noteworthy that the recommended dosage of allopurinol as stated in the medical reference, Epocrates, is
100mg initially, with a titrated dosage increase of 100mg to the maximum dosage of 600mg/day.\textsuperscript{2} The trials did not test subjects with the maximum dosage due to the restriction necessary for renal-impaired patients, as well as to the presumable fear of idiopathic kidney damage. Febuxostat was maximized at its 240mg dosage while the highest dose of allopurinol was 300mg amongst subjects without any renal impairment. This distorts the result because allopurinol was not tested at its maximized hypouricemic potential.

As displayed in Table 3, the serum uric acid levels were significantly reduced at a greater proportion in the febuxostat groups over the allopurinol groups of the FACT and APEX studies. Regardless of the fact that a considerable number of the subjects did not meet the primary outcome, claims were still made that febuxostat was superior to allopurinol. More importantly, as seen in the APEX study, when allopurinol’s efficacy was rendered completely unsuccessful amongst the subjects with renal impairment, febuxostat remained effective without causing any renal effects.

Allopurinol is a xanthine oxidase inhibitor which acts on the catabolic pathway from hypoxanthine to urate. Febuxostat acts very much in the same manner of Allopurinol, however, unlike the latter, Febuxostat is not purine-like in structure nor does it affect any other enzymes in the purine and pyrimidine pathways. In essence, febuxostat is a more selective xanthine oxidase inhibitor, and the difference could give the ability to treat with renal-impaired patients (febuxostat treatment) versus a possibility of unsuccessful treatment causing idiopathic harm (allopurinol treatment).

The secondary endpoint, the measurement of gout flares and tophi resolution are of greater \textit{clinical} importance. Patients will present to clinic more commonly with acute
gout flare pain and the production of tophi due to hyperuricemia rather than asymptomatic hyperuricemia. Randomized controlled trial evidence showed that, even though more febuxostat recipients achieved the serum uric acid endpoint of <6.0 mg/dL, this did not equate to an advantage over allopurinol in the clinically evident outcomes of acute gout flares and gout tophi reduction. In the FACT study, acute gout flares were reduced to as low as 8% and 6% in febuxostat groups versus 11% in the allopurinol 300mg group signifying no clear-cut divergence between the treatments. Moreover, the same trend was found within the subjects for the outcome of gout tophi reduction. Similarly, the APEX study also showed no statistically significant differences across treatment groups for both the secondary outcomes of acute gout flares and tophi reduction.

In terms of cost, febuxostat 40mg and 80mg is currently distributed for approximately $160.00 per month of medication, while allopurinol 300mg (one tablet daily) has been currently seen selling for $22.99 for 100 tablets.26 Besides economic feasibility, the adverse effects of drug administration are non economic costs. Both the APEX and FACT studies claimed the adverse effects and events were similar across treatment groups including notably concern-causing abnormal liver function results. Further studies that can concentrate on, or isolate the immediate and long-term effects of febuxostat on liver function need to be accomplished to further ensure safety in the administration of the drug. At this point, the makers of febuxostat recommend laboratory assessment of liver function at 2 and 4 months following initiation, and periodically thereafter.9
**Conclusion / Recommendations**

Based on the literature review completed, febuxostat proved to be more effective in reducing the serum uric acid concentration in subjects with hyperuricemia and gout. However, despite febuxostat’s success in contrast with allopurinol, the resolution of the clinical symptoms of acute gout flares and tophi showed that febuxostat had no significant advantage over its challenger. A crucial difference between the two drugs is that the dosage of allopurinol will have to be adjusted when treating renal-impaired individual. Febuxostat showed promising hypouricemic effects among those individuals tested with renal-impairment, distancing itself from allopurinol. Due to the recentness of FDA approval and unfamiliarity in the clinic setting, further observations of febuxostat’s long term efficacy and safety need to be done on a greater number of gout and hyperuricemic patients.
Figures & Tables

Figure 1- The development of gout in terms of sources and excretion.

Figure 2 – Simplified pathway of uric acid metabolism with mechanisms of discussed gout medications. Uricosuric drugs block the tubular reabsorption of filtered urate in the kidneys. Febuxostat and allopurinol inhibit the enzyme xanthine oxidase.
<table>
<thead>
<tr>
<th>Author</th>
<th>Published</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Treatments Studied</th>
<th>Outcomes</th>
<th>Final Comments</th>
</tr>
</thead>
</table>
| Khosravan, R.   | 2008      | Phase I Parallel-group Multiple-dose Open-label | n=96        | • Oral Febuxostat 80mg (4 x 20mg tabs daily for 7 consecutive days following an overnight fast ≥ 8 hrs  
  • Effect of Age and Gender on Febuxostat | • The pharmacokinetics, pharmacodynamics, and safety of Febuxostat do not appear to be substantially affected by age or gender following multiple dosing for 7 days | • No dose adjustment based on gender or age alone is necessary  
  • Small sample size                                                                 |
| Khosravan, R.   | 2007      | Phase I Randomized Single Center Crossover study | n=92        | • Single Febuxostat 40mg (n=24) Vs. Multiple Febuxostat 80mg (n=24) Vs.  
  Single Febuxostat 120mg (fasting and nonfasting conditions) (n=20) Vs.  
  Single Febuxostat 80mg (alone or with antacid) (n=24)  
  • Effect of Food or Antacid on Febuxostat | • Food—caused reduction in plasma concentration, rate and extent of absorption  
  • Author claims decrease not associated with clinically significant change is pharmacodynamic effect.  
  • Antacid—caused a decrease in the absorption rate, but no effect on the extent of absorption | • Febuxostat can be administered regardless of food or antacid intake  
  • Small sample size                                                                 |
| Khosravan, R.   | 2006      | Phase I Randomized Single-Center Open-Label Multiple-dose 3-period Crossover studies | Study 1: n=26 Study 2: n=25 | • Study 1: 5 days Febuxostat 80mg daily Vs. Feb 80mg daily + Indo 50mg BID Vs  
  Indomethacin 50mg BID  
  • Study 2: 7 days long Febuxostat 80mg daily | • Febuxostat had no effect on plasma pharmacokinetics of both indomethacin and naproxen.  
  • Indomethacin had no effect on plasma pharmacokinetics of febuxostat | • Febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khosravan, R. 2006</td>
<td>Phase I Parallel-group Open-label, Multiple-dose</td>
<td>n=26 Female and male 30-70yo Hepatic function: 11 = Normal 08 = Mild 08 = Moderate</td>
<td>Febuxostat 80mg daily x 7 days</td>
<td>No statistically significant differences in plasma pharmacokinetic parameters for febuxostat between subjects with mild or moderate hepatic impairment vs. with normal hepatic function. Serum uric acid percentage decrease lower in hepatic impaired vs. normal hepatic groups. Author claims not clinically significant.</td>
</tr>
<tr>
<td>Khosravan, R. 2006</td>
<td>Phase I Randomized Double-blind Placebo-controlled</td>
<td>n= 12 Female and male 18-55 yo</td>
<td>Febuxostat 10, 20, 30, 40, 50, 70, 90, 120, 160, 180, 240mg daily for 14 days</td>
<td>Percentage decrease in serum uric acid concentrations ranged from 27% to 76% for all doses and was dose linear for 10-</td>
</tr>
</tbody>
</table>

**Vs. Feb 80mg daily + Nap 500mg BID Vs. Naproxen 500mg BID**
- Effect of Febuxostat on pharmacokinetics of NSAIDS (indomethacin and naproxen) and vice versa.
- Naproxen caused increase in exposure to febuxostat, however author claims not clinically significant.
- Small sample size.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Design</th>
<th>Goals</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter Multiple-dose Dose-escalation study</td>
<td>Investigate the pharmacokinetics, pharmacodynamics and safety of Febuxostat over range of oral doses in healthy subjects</td>
<td>120mg per day dosage range. Majority of adverse events were mild-to-moderate in intensity. Febuxostat was well tolerated at once-daily doses of 10-240mg.</td>
<td></td>
</tr>
<tr>
<td>Mayer, M. 2005 Phase I Parallel-group Open-label Multiple-dose study</td>
<td>n=31 Female and male 26-76 yo Renal function: 11 = Normal 06 = mild 07 = moderate 07 = severe impairment</td>
<td>Febuxostat 80mg daily x 7 days. Study the safety, pharmacokinetics, and pharmacodynamics of Febuxostat in subjects with varying renal impairment.</td>
<td></td>
</tr>
<tr>
<td>Becker, M.A. 2005 Phase II Randomized Multicenter Double-blind Placebo-controlled Dose-response Clinical Trial</td>
<td>n=153 Female and male Ave age range =52.2yo-56.2yo 37 =40mg Feb 40 =80mg Feb 38 =120mg Feb</td>
<td>Febuxostat 40mg, 80mg, 120mg Vs. Placebo 28-days Degree of serum uric acid reduction was significantly greater in all Febuxostat treatment groups compared to placebo by day 7 and maintained over the 28-day study period. Data suggested therapeutic dosages likely to fall in</td>
<td></td>
</tr>
</tbody>
</table>

Febuxostat appears to be safe and well tolerated. Febuxostat was extensively metabolized and renal function did not seem to play an important role in elimination from the body. Febuxostat does not appear to require dose adjustments based on differences in renal function.
| Becker, M.A. | 2004 | Phase I Multiple-dose Placebo-controlled Dose-escalation study | n=154 Female and male 19-54 yo | Febuxostat 10, 20, 30, 40, 50, 70, 90, 120, 160, 180, 240mg daily for 14 days Vs. Febuxostat 30mg or Placebo BID  
- Determine the safety, tolerability, pharmacokinetics, pharmacodynamics of Febuxostat over range of oral doses in healthy volunteers | Febuxostat effectively decreased serum uric acid concentration in a dose-linear manner with once-daily dosing of up to 120mg.  
- Doses in excess of 120mg daily did not appear to provide significant additional hypouricemic effects.  
- Febuxostat did not appear to cause significant reduction in total purine synthesis  
- Sole mechanism of action of febuxostat confirmed as a xanthine oxidase inhibitor | Febuxostat is safe and well-tolerated when subjects were administered with drug in this study  
- Febuxostat effectively decreased serum uric acid concentration in a dose-linear manner with once-daily dosing of up to 120mg. |

Table 1 – Studies conducted to assess solely Febuxostat (Preapproval of FDA)
<table>
<thead>
<tr>
<th>Author</th>
<th>Published</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Treatments Studied</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Schumacher Jr., H.R. MD | 2009      | Cohort Open Label Non-Random Uncontrolled (FOCUS) | n=116 08 = 40mg 79 = 80mg 29 = 120mg -58 DC prematurely -38 DC first year -13 ADR | Febuxostat 40mg, 80mg, 120mg PO daily Time =5 years                                         | • 5 years -- 54/58 with sUA<6.0mg/dL  
• 5 years—18/26 complete resolution of tophus since baseline  
• No deaths  
• After 1st year of stable dose, subjects had <1 gout flare per year | • Long-term treatment with febuxostat resulted in durable maintenance of sUA <6.0 mg/dl for most subjects.  
• There was nearly complete abolition of gout flares in patients completing the study.  
• Baseline tophi resolved in a majority of subjects.  
| Wortmann, R.L.       | 2008      | Open Label RCT Extension of FACT and APEX trials (EXCEL) | n=1086                                                        | Febuxostat 80mg, 120mg, 240mg Vs. Allopurinol 300mg, 100mg (based on renal function) | • Taken from subjects from the APEX and FACT studies, the incidence of acute gout flares was reduced to < 1 per year by the 36th month of treatment amongst all drugs | • Continuation of APEX and FACT studies  
| Schumacher Jr., H.R. MD | 2008      | RCT Phase III Double-blind 167 sites US (APEX) | n=1072 (18-85 years of age with gout ≥8.0mg/dL) Completed: 101 = Placebo 174 = Feb 80mg 200 = Feb 120mg 086 = Feb 240mg 211 = Alo 300mg | Febuxostat 40mg, 80mg, 120mg, 240mg Vs. Allopurinol 300mg, 100mg (based on renal function) Vs. Placebo Daily | • sUA <6.0mg/dL in last 3 months (no renal impairment)  
36% = Febuxostat 80mg  
52% = Febuxostat 120mg  
66% = Febuxostat 240mg  
10% = Allopurinol (P<0.001) = Greater febuxostat proportion achieved primary end point | • Predominantly Men (Ave. 93.6% Men)  
• Uncertain if health care administrations and staff were blinded to study as well due to absence of explicit explanation by |
<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>sUA &lt;6.0mg/dL vs. allopurinol or placebo</th>
</tr>
</thead>
</table>
| renal impairment | 44% = Febuxostat 80mg  
-52% = Febuxostat 120mg  
-66% = Febuxostat 240mg  
00% = Allopurinol 100mg for renal impairment |
| no renal impairment | 76% = Febuxostat 80mg  
87% = Febuxostat 120mg  
94% = Febuxostat 240mg  
41% = Allopurinol 300mg  
01% = Placebo  
00% = Allopurinol 100mg for renal impairment |

- % reduction in sUA at final visit:  
- Proportion requiring treatment for gout flare (wks 8-28):  
- No statistically significant differences between treatment groups.
- Total # and size of tophi
  No significant differences in # of tophi between treatment groups

  No significant differences in median tophus size between treatment groups

  Mean % decrease with Febuxostat 120mg (-1.2) versus placebo (-0.3) at week 28 (P≤0.05)

- **Adverse Events**
  Occurred in similar frequency across treatment groups

  Statistically significant increase of diarrhea in febuxostat 240mg.

  Included: URIs, abnormal liver-function test results, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms.

- **Abnormal liver-function results**—
  17/51 (6%)= 80mg Feb
  10/51 (4%)= 120mg Feb
  06/51 (4%)= 240mg Feb
  15/51 (6%)=300mg Allo
<table>
<thead>
<tr>
<th>Becker, M.A. MD</th>
<th>2005</th>
<th>RCT Phase III 52-week Multicenter (FACT)</th>
<th>n=762</th>
<th>Febuxostat 80mg Vs. Febuxostat 120mg Vs. Allopurinol 300mg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Included in efficacy analysis:</td>
<td></td>
<td>53% = 80mg Febuxostat 62% = 120mg Febuxostat 21% = 300mg Allopurinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>255 = Feb 80mg</td>
<td></td>
<td>Reached primary endpoint of study by higher proportions of febuxostat-treated subjects than allopurinol-treated subjects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 = Feb 120mg</td>
<td></td>
<td>• By weeks 49-52 (final visit interval) flare incidence:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>251 = Alo 300mg</td>
<td></td>
<td>08% = 80mg Febuxostat 06% = 120mg Febuxostat 11% = 300mg Allopurinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Median % Reduction in tophus area amongst 156</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Large sample size</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Uncertain if health care administrations and staff were blinded to study as well due to absence of explicit explanation by author.</td>
</tr>
</tbody>
</table>

- 03/51 (2%)= Placebo
- • 12 withdrew due to abnormal LFT
- 05 = Febuxostat 80mg
- 03 = Febuxostat 120mg
- 04 = Allopurinol 300mg
- • Adverse events leading at least to study discontinuation occurred in 78 subjects with similar frequency across treatments
- • 8 withdrew due to diarrhea


Becker, M.A. MD 2005 RCT Phase III Double-blind 52-week Multicenter (FACT) n=762 Included in efficacy analysis: 255 = Feb 80mg 250 = Feb 120mg 251 = Alo 300mg

Febuxostat 80mg Vs. Febuxostat 120mg Vs. Allopurinol 300mg Daily

Time = 52-Week Trial

- Compared the safety and efficacy of febuxostat with the safety and efficacy of allopurinol in adult subjects with gout and sUA ≥8.0mg/dL
- sUA <6.0mg/dL
- 53% = 80mg Febuxostat 62% = 120mg Febuxostat 21% = 300mg Allopurinol

Reached primary endpoint of study by higher proportions of febuxostat-treated subjects than allopurinol-treated subjects.

- By weeks 49-52 (final visit interval) flare incidence:
- 08% = 80mg Febuxostat 06% = 120mg Febuxostat 11% = 300mg Allopurinol
- Median % Reduction in tophus area amongst 156
subjects with tophi from baseline:
83% = 80mg Febuxostat
66% = 120mg Febuxostat
50% = 300 mg Allopurinol

No statistically significant differences among the groups in the percentage reduction in tophus area or in reduction in number of tophi

- Incidence of adverse effects:
  Similar in the three treatment groups

  Included: abnormal liver-function test results, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms.

  Mild to moderate in severity.

  Incidence of serious adverse effects similar in all groups. Serious adverse effects occurred in 51 subjects, 34/51 continued the study with resolution.

- Most common adverse event leading to withdrawal from study:
### Abnormal liver-function results—
05/256 = 80mg Febuxostat  
07/251 = 120mg Febuxostat  
01/253 = 300mg Allopurinol  
(P=0.04 comparing 120mg Feb. vs. 200mg Allo)

Table 2—Trials comparing Febuxostat versus Allopurinol including long-term trials of Febuxostat usage.
<table>
<thead>
<tr>
<th>Indicated outcome target</th>
<th>FACT Study</th>
<th>APEX Study</th>
<th>FOCUS Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric Acid Level</td>
<td>sUA &lt;6.0mg/dL</td>
<td>sUA &lt;6.0mg/dL in last 3 months (no renal impairment)</td>
<td>sUA&lt;6.0mg/dL</td>
<td>Overall, febuxostat displayed a greater amount of uric acid reduction among the test subjects</td>
</tr>
<tr>
<td></td>
<td>53% = 80mg Febuxostat</td>
<td>36% = Febuxostat 80mg</td>
<td>54/58 (93%) = Across all febuxostat dosages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62% = 120mg Febuxostat</td>
<td>52% = Febuxostat 120mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21% = 300mg Allopurinol</td>
<td>66% = Febuxostat 240mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reached primary endpoint of study by higher proportions of febuxostat-treated subjects than allopurinol-treated subjects.</td>
<td>10% = Allopurinol 300mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(P&lt;0.001) for comparison of each febuxostat group with the allopurinol group</td>
<td>(P&lt;0.001) = Greater febuxostat proportion achieved primary end point &lt;6.0mg/dL vs. allopurinol or placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sUA &lt;6.0mg/dL in last 3 months (renal impairment)</td>
<td>sUA &lt;6.0mg/dL at 28-week and final visit (no renal impairment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44% = Febuxostat 80mg</td>
<td>76% = Febuxostat 80mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46% = Febuxostat 120mg</td>
<td>87% = Febuxostat 120mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>60% = Febuxostat 240mg</td>
<td>94% = Febuxostat 240mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>00% = Allopurinol 100mg</td>
<td>41% = Allopurinol 300mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% reduction sUA</td>
<td>01% = Placebo</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>-45% = Febuxostat 80mg</td>
<td>00% = Allopurinol 100mg for renal impairment</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-52% = Febuxostat 120mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute Gout Attacks / Flares</strong></td>
<td><strong>By weeks 49-52 (final visit interval) flare incidence:</strong> 08% = 80mg Febuxostat 06% = 120mg Febuxostat 11% = 300mg Allopurinol</td>
<td><strong>Proportion requiring treatment for gout flare (wks 8-28):</strong> No statistically significant differences between treatment groups</td>
<td><strong>After 1st year of stable dose, subjects had &lt;1 gout flare per year</strong></td>
<td><strong>Despite febuxostat’s success in contrast with allopurinol, the resolution of the clinical symptoms of acute gout flares and tophi showed that febuxostat had no significant advantage over its challenger.</strong></td>
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<td>---</td>
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</tr>
<tr>
<td><strong>Gout Tophi Reduction</strong></td>
<td><strong>Median % Reduction in tophus area amongst 156 subjects with tophi from baseline:</strong> 83% = 80mg Febuxostat 66% = 120mg Febuxostat 50% = 300 mg Allopurinol No statistically significant differences among the groups in the percentage reduction in tophus area or in reduction in number of tophi</td>
<td><strong>Total # and size of tophi:</strong> No significant differences in # of tophi between treatment groups No significant differences in median tophus size between treatment groups Mean % decrease with Febuxostat 120mg (-1.2) versus placebo (-0.3) at week 28 (P≤0.05)</td>
<td><strong>Tophi after 5 years:</strong> 18/26 (69%) = Complete resolution of tophus since baseline</td>
<td><strong>Same as above</strong></td>
</tr>
<tr>
<td><strong>Quality of life (as reported by subjects in study)</strong></td>
<td>Not reported by subjects</td>
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<td>Subjects without hyperuricemia do not suffer from its supersaturation effects More extensive study necessary</td>
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<tr>
<td><strong>Drug Adverse Effects (as reported by study)</strong></td>
<td><strong>Incidence of adverse effects:</strong> Similar in the three treatment groups Included: abnormal liver-function test results, diarrhea, headaches, joint-related signs and symptoms,</td>
<td><strong>Incidence of adverse events:</strong> Occurred in similar frequency across treatment groups Included: URIs, abnormal liver-function test results, diarrhea, headaches, joint-related signs</td>
<td><strong>Incidence of adverse events:</strong> No deaths</td>
<td>Both the APEX and FACT studies claimed the adverse effects and events were similar across treatment groups including notably concern-causing abnormal liver function results.</td>
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</table>
and musculoskeletal and connective tissue signs and symptoms.

Mild to moderate in severity.

Incidence of serious adverse effects similar in all groups. Serious adverse effects occurred in 51 subjects, 34/51 continued the study with resolution.

Most common adverse event leading to withdrawal from study: Abnormal liver-function results—
- 05 = 80mg Febuxostat
- 07 = 120mg Febuxostat
- 01 = 300mg Allopurinol
(P=0.04 comparing 120mg Feb vs. 200mg Allo)

and symptoms, and musculoskeletal and connective tissue signs and symptoms.

Statistically significant increase of diarrhea in febuxostat 240mg.

- Abnormal liver-function results—
  - 17/51 (6%) = 80mg Feb
  - 10/51 (4%) = 120mg Feb
  - 06/51 (4%) = 240mg Feb
  - 15/51 (6%) = 300mg Allo
  - 03/51 (2%) = Placebo

  - 12 withdrew due to abnormal LFT

  - 05 = Febuxostat 80mg
  - 03 = Febuxostat 120mg
  - 04 = Allopurinol 300mg

Adverse events leading at least to study discontinuation occurred in 78 subjects with similar frequency across treatments

- 8 withdrew due to diarrhea

Further studies that can concentrate on, or isolate the immediate and long-term effects of febuxostat specifically on liver function need to be accomplished to further ensure safety in the administration of the drug.

At this point, the makers of febuxostat recommend laboratory assessment of liver function at 2 and 4 months following initiation, and periodically thereafter

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Table 3—Comparison of outcomes from clinical trials
References


