Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Joint Meeting

sNDA 21856: Febuxostat for the chronic management of hyperuricemia in patients with gout

FDA Opening Remarks

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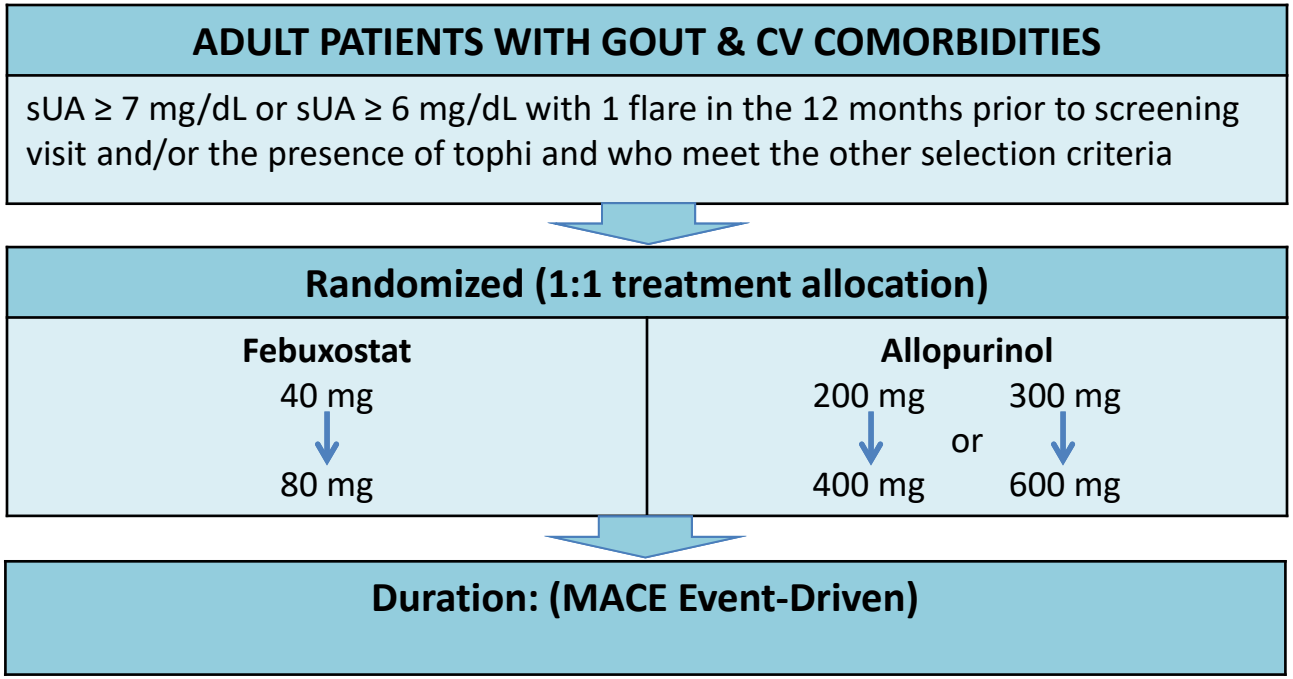
U.S. Food and Drug Administration
January 11, 2019

Febuxostat

- Mechanism of Action
  - Xanthine oxidase inhibitor (XOI)
- Approved Indication and Dosages (2009)
  - For the chronic management of hyperuricemia in patients with gout
  - 40-80 mg once daily
    - Outside U.S. approved at doses up to 120 mg once daily
- Current Labeled Warnings and Precautions
  - Increase in gout flares with initiation of therapy
  - Cardiovascular Events
  - Hepatic toxicity (including failure)
  - Serious Skin Reactions (Stevens-Johnson Syndrome [SJS], drug reaction with eosinophilia and systemic symptoms [DRESS], and Toxic Epidermal Necrolysis [TEN])

CARES Trial Design

Multi-national, Randomized, Double-blind, Active Controlled Cardiovascular Outcomes Trial



Primary Analysis of MACE

	Febuxostat N=3098 PY=8799.5	**Allopurinol** N=3092 PY=8675.7	**Hazard Ratio*** **(95% CI)**
MACE	**335** [3.8]	**321** [3.7]	**1.03 (0.89, 1.21)**
CV Death	134	100	1.34 (1.03, 1.73)
Non-fatal MI	111	118	0.93 (0.72, 1.21)
Non-fatal Stroke	71	70	1.01 (0.73, 1.41)
Unstable Angina with Urgent Coronary Revascularization	49	56	0.86 (0.59, 1.26)

PY=person-year
[ ]: incidence rate per 100 person-year
*HR for Febuxostat vs. Allopurinol

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Secondary Analysis: MACE Components

	Febuxostat N=3098 PY=8799.5	**Allopurinol** N=3092 PY=8675.7	**Hazard Ratio*** **(95% CI)**
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Benefit-Risk Assessment Considerations

- Factors for consideration when discussing potential regulatory actions for febuxostat
  - Febuxostat is effective urate lowering therapy (ULT)
  - Six ULTs are currently marketed
    - Each with their own various associated safety risks
  - Febuxostat is the only alternative XOI to allopurinol
    - XOIs are recommended first-line therapy for gout
  - Unmet medical need
  - Growing gout epidemic

Regulatory Actions for AC Discussion

- Strengthening current CV warning
- Add boxed warning for CV death
- Change indication to second line therapy
- Citizens Petition request to withdraw febuxostat from the market

Discussion Points

1. **DISCUSSION:** Discuss the results of the "Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)" study, particularly major adverse cardiovascular events (MACE) and cardiovascular (CV) mortality. Please consider the following in your discussion:
    a. Biological plausibility of CV mortality
    b. Strength of the findings for CV mortality, considering the totality of available data.

Discussion Points

2. **DISCUSSION:** Discuss the benefits of febuxostat for the treatment of hyperuricemia in patients with gout.
3. **DISCUSSION:** Given the results of the CARES study, discuss whether the benefit-risk profile of febuxostat for the treatment of hyperuricemia in patients with gout has changed. Address the following in your discussion:
    a. Discuss any patient populations in which the benefits outweigh the risks of the use of febuxostat
    b. Discuss any patient populations in which the benefits do not outweigh the risks of the use of febuxostat.

Discussion Points

4. **DISCUSSION:** Discuss the following potential regulatory activities in response to the results of the CARES study and the potential clinical impact of these options.
    a. Update existing warning regarding Cardiovascular Events in the febuxostat product label
    b. Addition of a boxed warning to the febuxostat product label
    c. Modify labeling to limit use of febuxostat to second line therapy (e.g. 2nd line therapy in patients who have failed allopurinol)
    d. Withdrawal of febuxostat from the market.

Voting Question

5. **VOTING:** Based upon the available data, is there a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout? (Yes/No)
    - If you voted "Yes", describe the patient population with a favorable benefit-risk profile for use of febuxostat. Also, describe any other recommendations (e.g. labeling changes) you may have for use of febuxostat in this population
    - If you voted "No", discuss your rationale, the impact of this recommendation, and any other recommendations you may have.


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Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Joint Meeting

sNDA 21856: Febuxostat for the chronic management of hyperuricemia in patients with gout

FDA Introduction and Regulatory History

Rosemarie Neuner, MD, MPH
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
January 11, 2019

Overview

- Current Gout Therapeutics
- Regulatory History for Febuxostat
- CARES Study
  - Study Design
  - Regulatory History
- Cardiovascular Safety Findings for CARES Study
- Drug Usage and Utilization
- Clinical Considerations and Benefit-Risk Assessment

Therapeutic Armamentarium in Gout

Product	Approved Dosing	Efficacy and Safety
First Line Therapy: Xanthine Oxidase Inhibitors (XOI)		
Allopurinol LASSO Study Febuxostat NDA at Drugs@FDA	100-800 mg/d; Doses >300 mg/d divide into twice daily (BID) administration	• 300 mg dose ~ 2 to 3.5 mg/dL* mean ↓sUA • Hypersensitivity reactions, cutaneous reactions, gastrointestinal intolerance
Febuxostat Febuxostat NDA at Drugs@FDA	40-80 mg daily (QD)	• 80 mg dose ~ 4.5 mg/dL* mean ↓sUA • CV risk, hepatoxicity, cutaneous reactions
Second Line Therapy: Uricosuric Agents		
Probenecid Pui et al, J Rheum 2013	500-1000 mg BID ($T_{1/2}$ 3-8 hrs)	• Mean 1.3 g/d dose ~ 2.9 mg/dL* mean ↓sUA • Nephrolithiasis
Lesinurad Zurampic NDA at Drugs@FDA	200 mg QD with concomitant XOI	• 200 mg dose ↓sUA on background XOI ~ 1 mg/dL mean • Renal events including failure, CV risk
Lesinurad/Allopurinol FDC Duzallo NDA at Drugs@FDS	LES200mg/ALLO200 mg QD or LES200mg/ALLO300 mg QD	• Same safety issues as with lesinurad and allopurinol
Third Line Therapy: Uricase		
Pegloticase Krystexxa NDA at Drugs@FDA	8 mg every 2 weeks intravenously (IV)	• Mean ↓sUA ~6.6 to 6.8* mg/dL • Anaphylaxis, infusion reactions, ↑CHF

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Febuxostat (Uloric®)

- **Mechanism of Action**
  - Selective xanthine oxidase inhibitor
- **Approved Indication and Dosage**
  - For the chronic management of hyperuricemia in gout
  - 40-80mg once daily
    - Outside U.S. approved at doses up to 120 mg once daily
- **Current Labeled Warnings and Precautions**
  - Increase in gout flares with initiation of therapy
  - Cardiovascular Events
  - Hepatic toxicity (including failure)
  - Serious Skin Reactions (Stevens-Johnson Syndrome [SJS], drug reaction with eosinophilia and systemic symptoms [DRESS], and Toxic Epidermal Necrolysis [TEN])

Relevant Regulatory History

- Febuxostat was approved in 2009 following 3 review cycles including an Arthritis Advisory Committee meeting focused on the drug's cardiovascular (CV) safety
  - Pivotal trials were active and placebo controlled studies of 6 -12 months duration
  - Active comparator was allopurinol at 100-300 mg once daily
  - Pivotal studies utilized a surrogate primary endpoint based on number of patients achieving a sUA $\leq$ 6mg/dL
  - Incidence of gout attacks and reduction in tophi were evaluated as secondary endpoints
  - Complete response action for 2 cycles based upon CV safety concerns

Relevant Regulatory History (cont'd)

- First Review Cycle – Complete Response
  - Cardiovascular signal
- Febuxostat-treated subjects as compared to allopurinol or placebo patients had
  - Higher rate of overall mortality
  - Higher rate of mortality due to CV causes
  - Higher rate of cardiovascular thromboembolic events

Relevant Regulatory History (cont'd)

- Second Review Cycle – Complete Response
- Persistent concerns related to CV safety and mortality
- Re-analysis and post hoc adjudication
  - APTC criteria of all serious CV events from original safety database and new safety data from 2 ongoing, long-term extensions (LTEs)
  - Persistent imbalance in all-cause mortality and investigator reported primary APTC not in favor of febuxostat
- Concerns regarding
  - Insufficient data for post hoc application of APTC criteria or to confirm events
  - Lack of dose response for CV events
  - Limited exposure to allopurinol due to unequal randomization in controlled portions of studies followed by most patients receiving open-label febuxostat in LTE

Second Review Cycle: All-Cause Mortality in Febuxostat Safety Database by Patient-Years of Exposure

Treatment	P-Y Exposure	Number of Deaths	Rates/100 P-Y	95% CI
Phase 3 Randomized Controlled Studies				
Febuxostat Total	671	4	0.60	0.16-1.53
Allopurinol 300/100 mg QD	334	0	0.0	0.00-1.11
Long-Term Extension Studies				
Febuxostat Total	2121	8	0.38	0.16-0.74
Allopurinol 300/100 mg QD	145	0	0.0	0.00-2.54
Phase 3 Randomized Controlled and Long-Term Extension Studies				
Febuxostat Total	2792	12	0.43	0.22-0.75
Allopurinol 300/100 mg QD	479	0	0.0	0.00-0.77

Note: No deaths in phase 1 or during treatment in phase 2 controlled studies; Confidence intervals (CI) calculated via Poisson distribution
(Data Cut-Off February 2006)

- Nine of the 12 deaths were cardiovascular
- Imbalances in all-cause mortality could not be explained by differences in duration between treatment groups

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Relevant Regulatory History (cont'd)

- Sponsor next conducted a new safety and efficacy study
  - Phase 3, non-inferiority, randomized, double-blind, active controlled trial
  - Larger (N=2269) than previous two phase 3 studies combined (N=1832)
  - 3 x more subjects randomized to active control arm (allopurinol; n=765) than combined phase 3 studies (combined allopurinol; n=521)
  - Included approximately 1300 subjects at risk for CV disease
  - Had pre-specified CV endpoints and CV adjudication committee
- Numerically more deaths in allopurinol vs. febuxostat group (3 vs. 2)
  - Results suggested risk of CV events with febuxostat were the same or lower than with allopurinol

Relevant Regulatory History (cont'd)

- Arthritis Advisory Committee Meeting (11/2008)
  - Voted to recommend approval of febuxostat (12 to 0 with 1 abstention)
  - Recommended a postmarketing (PMR) study to further assess the CV risk associated with drug
- Approval letter required Applicant (2/2009)
  - To conduct a "randomized, controlled trail of adequate size and duration to determine whether the use of [febuxostat] is associated with moderate increase the risk for serious adverse cardiovascular outcomes as compared to allopurinol"
  - Include following warning in drug's label

"Cardiovascular Events: In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y[95% CI 0.16-1.53]). A causal relationship with ULORIC has not been established. Monitor of signs and symptoms of MI and stroke."

Relevant Regulatory History: CARES Study

- Multicenter, randomized, double blind, CV outcome study conducted in US, Canada and Mexico in hyperuricemic subjects with gout and major CV disease
- Primary endpoint: composite of major adverse CV events (MACE)
- Secondary endpoints: individual components of MACE and death from any cause
- Non-inferiority trial design
  - To accrue 624 MACE events with 90% power to reject a hazard ratio risk margin for MACE (febuxostat vs allopurinol) greater than 1.3 at one-sided 2.5% alpha level assuming a true hazard ratio of 1.0

CARES: Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity

Relevant Regulatory History: CARES Study

- Doses of both ULTs were ↑ to maximum doses of 80 mg QD febuxostat and 600 mg QD allopurinol based on achieving sUA level <6 mg/dL and renal function
- Subjects received prophylactic gout therapy during the first 6 months
  - Either colchicine, naproxen or another NSAID, or prednisone
- Timeline extension given due to study enrollment difficulties
  - Added sites in Mexico and Canada
- Study was completed in May 2017

NSAID: Non-steroidal anti-inflammatory drug

Relevant Regulatory History (cont'd)

- Drug Safety Communication (DSC) issued November 2017 when initial results of CARES were available
- Final study report submitted January 2018
  - Applicant has proposed an updated CV warning in product's labeling
  - Study published in NEJM March 2018
  - Data also presented at
    - American Academy of Cardiology Annual Meeting (March 2018)
    - American College of Rheumatology Annual Meeting (October 2018)
- Citizen's Petition submitted by Public Citizen to withdraw febuxostat from market based on CARES data (June 2018)
- Updated DSC issued August 2018 regarding ongoing agency review of CARES study and plans to hold AC meeting in early 2019 to discuss results of CARES

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Statistical Assessment of Cardiovascular Safety of CARES

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Statistical Reviewer
Division of Biometrics VII/Office of Biostatistics
U.S. Food and Drug Administration
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Characteristics of Febuxostat and Allopurinol Users in Real World Settings and Utilization Patterns

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U.S. Food and Drug Administration
January 11, 2019

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Clinical Considerations and Benefit-Risk Assessment

Rosemarie Neuner, MD, MPH
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
January 11, 2019

CARES Study: Clinical Considerations

- CARES results
  - Excluded pre-specified non-inferiority margin for MACE
  - Shows significant increase in CV death
    - Majority of CV deaths occurred following discontinuation of study treatment
    - No clear cause of increase in CV death
- Mechanism of action for increased risk in CV death not clear
- CARES enrolled high risk patient population
  - Generalizability to gout patients in real world settings is unclear
- Allopurinol is the most commonly dispensed Xanthine Oxidase Inhibitor (XOI)

Other Gout CV Outcome Studies

- FAST: Febuxostat versus Allopurinol Streamlined Trial
  - Cardiovascular Outcome Trial (CVOT) required by EMA
  - Phase 4, randomized, open-label, blinded endpoint study conducted primarily in the United Kingdom and Denmark in hyperuricemic patients with at least one other CV risk factor
  - "Treat to target" dosing (sUA<6md/dL)
    - Optimization of allopurinol (based on renal function)
    - Febuxostat dosed at 80 or 120 mg/day
  - Primary endpoint: composite of major adverse CV events (MACE) (Adjudicated)
  - Completed enrollment (N=6,142); key results available May 2020

- VA is conducting a comparative effectiveness gout study with febuxostat versus allopurinol
  - Collected safety data may contain additional data regarding CV risk associated with febuxostat

Benefit-Risk Assessment Considerations

Benefit Assessment Considerations

- Febuxostat is an efficacious urate lowering therapy
  - Can be used as an effective agent in “treat-to-target” dosing management of hyperuricemic gout patients recommended by current treatment guidelines
  - No dose adjustment necessary in patients with
    - Mild to moderate hepatic impairment
    - Mild to moderate renal impairment
      - Dose limited to 40 mg once daily in patients with severe renal impairment
  - An alternative for patients unable to tolerate allopurinol
  - Different drug-drug interaction (DDI) considerations than allopurinol
  - XOI class of ULT are potent and administration is less problematic than other ULT

Risk Assessment Considerations

- Febuxostat's safety profile includes
  - Serious skin reactions
    - Stevens-Johnson Syndrome [SJS], drug reaction with eosinophilia and systemic symptoms [DRESS], and Toxic Epidermal Necrolysis [TEN])
  - Hepatic events including hepatic failure
  - Cardiovascular events, including CV death

Context of Use Considerations

Product	Approved Dosing	Efficacy and Safety
First Line Therapy: Xanthine Oxidase Inhibitors (XOI)		
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Benefit-Risk Assessment

- Factors for consideration when discussing potential regulatory actions for febuxostat
  - 6 urate lowering therapies (ULTs) are currently marketed
    - Two will no longer be available as of 2/1/19 (https://www.zurampic.com)
    - Each with their own various associated safety risks
  - Febuxostat is the only alternative XOI to allopurinol
    - XOIs are recommended first-line therapy for gout
  - Unmet medical need
  - Growing gout epidemic

Regulatory Actions for AC Discussion

- Strengthening current CV warning
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- Change indication to second line therapy
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Acknowledgements

- ***DPARP***

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Outline

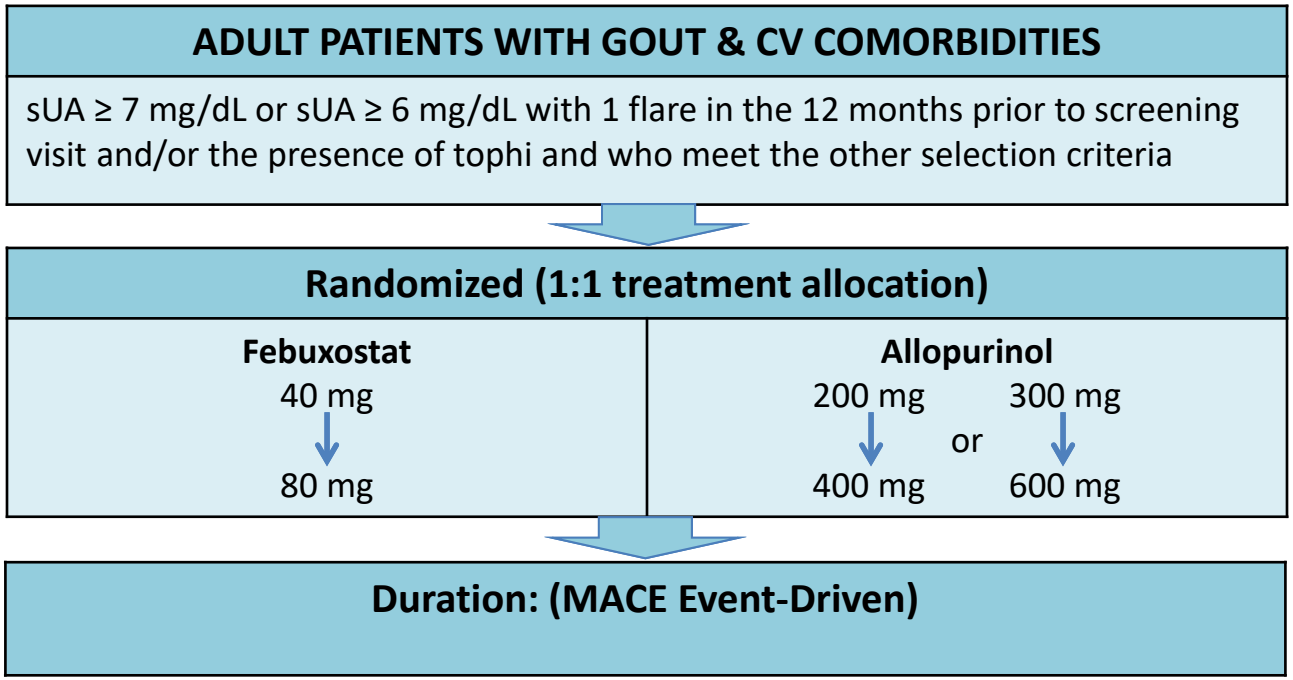
- Trial Objective and Design
- Statistical Methods
- Results
- Summary

Primary Objective

- To rule out a hazard ratio of MACE greater than 1.3 associated with febuxostat relative to allopurinol
- Three interim analyses and a final analysis
- Results of the final analysis are presented. All confidence intervals are at the nominal 95% level
- Primary Major Adverse Cardiovascular Event (MACE) composite
  - Cardiovascular (CV) death
  - Non-fatal myocardial infarction (MI)
  - Non-fatal stroke
  - Unstable angina with urgent coronary revascularization

CARES Trial Design

MULTI-NATIONAL, RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED CARDIOVASCULAR OUTCOME TRIAL



Trial Disposition and Treatment Exposure

	Febuxostat N=3098	Allopurinol N=3092
Trial Completion		
Completed	1704 (55.0%)	1706 (55.2%)
Lost to Follow-up	226 (7.3%)	223 (7.2%)
Withdrawal	595 (19.2%)	587 (19.0%)
Other	573 (18.5%)	576 (18.6%)
On-Study Follow-up		
Median (years)	2.7	2.6
Maximum (years)	6.9	7.0
≥ 2 yrs (%)	60.9%	59.8%
Treatment Exposure*		
Median (years)	2.0	2.0

*All randomized subjects exposed to at least one dose of randomized treatment

Trial Subjects Vital Status

	Febuxostat N=3098	Allopurinol N=3092
Completed Trial	1704	1706
Alive	1461 (86%)	1507 (88%)
Dead	243 (14%)	199 (12%)
Discontinued Trial*	1394	1386
Alive	878 (63%)	882 (64%)
Dead	89 (6%)	110 (8%)
Unknown	427 (31%)	394 (28%)

*The applicant updated subjects' vital status based on public records

Baseline Characteristics

	Febuxostat N=3098	Allopurinol N=3092
Age, Mean ± SD, yrs	64.6 ± 8.6	65.0 ± 8.5
Male	84%	84%
White	70%	69%
Randomized in US	86%	86%
History of Diabetes	55%	55%
History of CHF	20%	20%
Hypertension	92%	92%
Hyperlipidemia	86%	87%
Year of Gout Diagnosis[a]		
< 5	37%	35%
5-10	19%	20%
> 10	44%	45%
Renal Function Status[a]		
Normal	8%	7%
Mild Impairment	39%	40%
Moderate Impairment	53%	53%
BMI, Mean ± SD, kg/m^2	33.6 ± 7.0	33.4 ± 6.9

SD = standard deviation; CHF= congestive heart failure; BMI = body mass index

[a] The calculation ignored missing values

Outline

- Trial Objective and Design
- **Statistical Methods**
- Results
- Summary

Statistical Analysis Method (1)

Endpoints

- **Primary**: MACE composite (CV Death, non-fatal MI, non-fatal stroke, unstable angina with urgent coronary revascularization)

- **Secondary:**
  - Individual components of the primary MACE
  - Antiplatelet Trialists' Collaborative (APTC): composite of CV Death, non-fatal MI, and non-fatal stroke
  - All-Cause death
  - All-Cause death (on-treatment + 30 days)

Statistical Analysis Method (2)

- **Analysis Population**

  All randomized subjects exposed to at least one dose of randomized treatment, followed from the time of randomization to the last recorded study visit (on-study)

- **Censoring**

  On-study analysis included all events in the trial (on- and off-treatment periods)

- **Type I error rate: $\alpha = 0.05$ (two-sided)**

  Confidence intervals for all endpoints are presented at 95% confidence level

- **Time to Event Analysis**

  Cox proportional hazards model, with treatment as covariate, stratified by baseline renal function status

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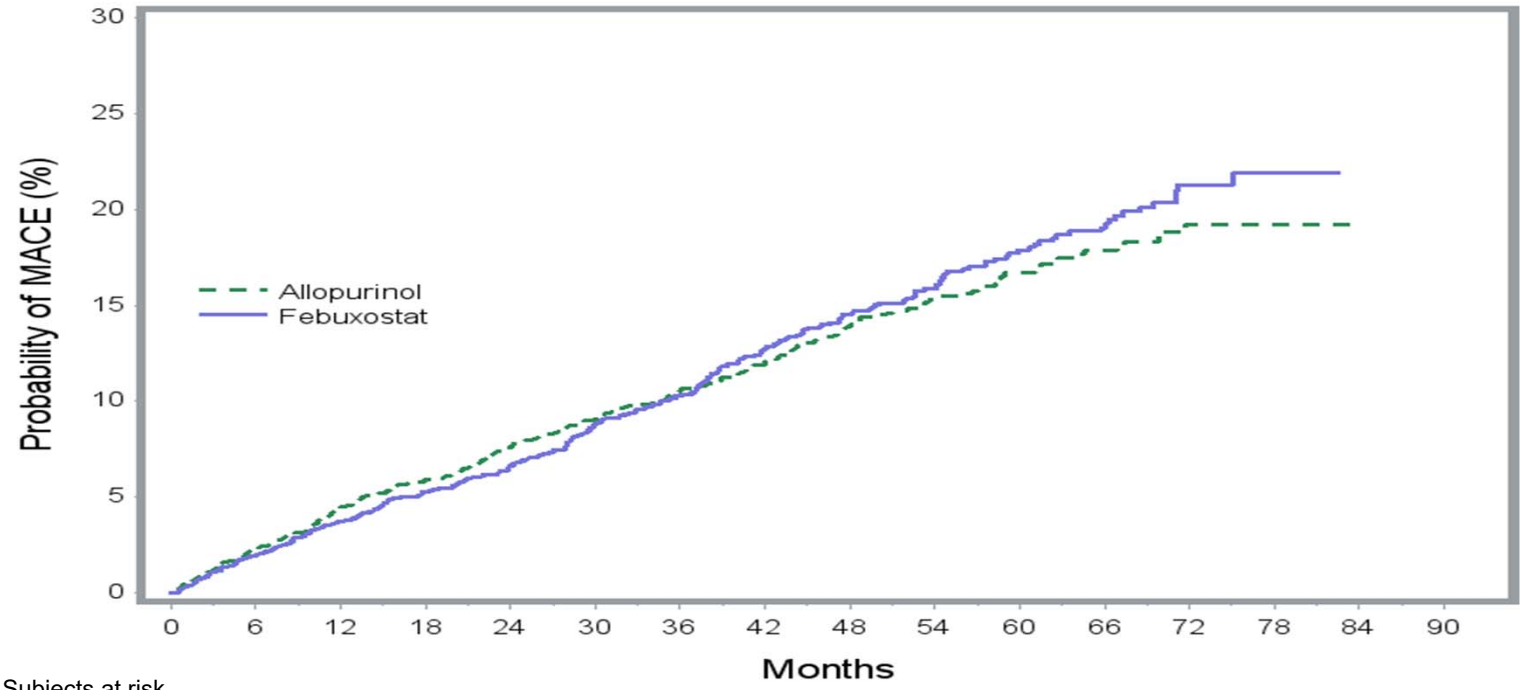
Primary Analysis of MACE

	Febuxostat N=3098 PY=8799.5	**Allopurinol** N=3092 PY=8675.7	**Hazard Ratio*** **(95% CI)**
MACE	**335** [3.8]	**321** [3.7]	**1.03 (0.89, 1.21)**
CV Death	134	100	1.34 (1.03, 1.73)
Non-fatal MI	111	118	0.93 (0.72, 1.21)
Non-fatal Stroke	71	70	1.01 (0.73, 1.41)
Unstable Angina with Urgent Coronary Revascularization	49	56	0.86 (0.59, 1.26)

PY=person-year
[ ]: incidence rate per 100 person-year
*HR for Febuxostat vs. Allopurinol

Kaplan-Meier Plot of MACE



Subjects at risk

Febuxostat	3098	2776	2478	2081	1817	1552	1339	1120	919	739	541	404	207	48	0
Allopurinol	3092	2761	2444	2048	1766	1516	1324	1093	887	725	554	390	211	48	0

MACE On-Treatment vs. After-Treatment

	Febuxostat			Allopurinol		
	Events	PY*	IR**	Events	PY*	IR**
On-Study	**335**	**8799.5**	**3.8**	**321**	**8675.7**	**3.7**
On-Treatment	191	7299.3	2.6	199	7143.7	2.8
After-Treatment Discontinuation	144	1500.2	9.6	122	1532.0	8.0

*PY=person-year; **IR= incidence rate per 100 person-year

Secondary Analysis:
Individual Components of MACE

	Febuxostat N=3098 PY=8799.5	**Allopurinol** N=3092 PY=8675.7	**Hazard Ratio*** **(95% CI)**
MACE	335 [3.8]	321 [3.7]	1.03 (0.89, 1.21)
CV Death	**134**	**100**	**1.34 (1.03, 1.73)**
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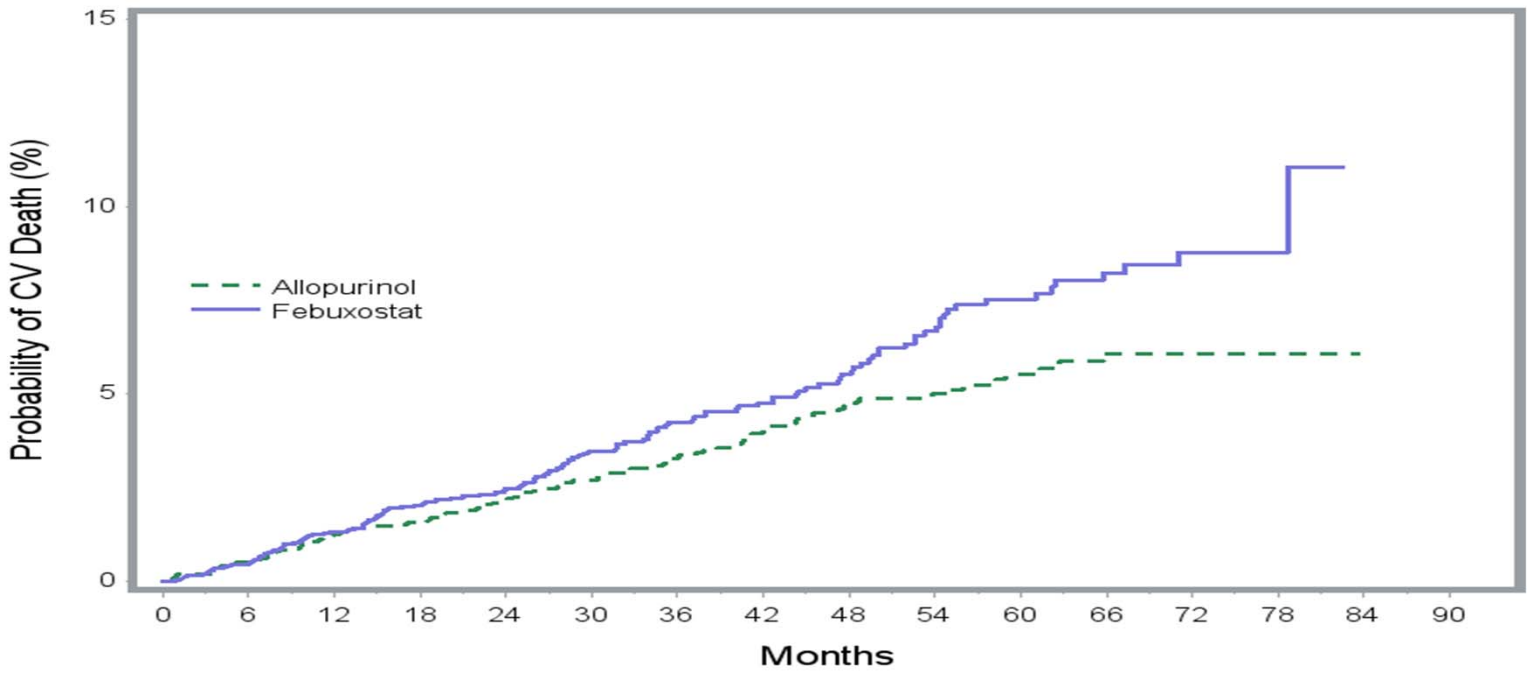
PY=person-year; [ ]: incidence rate per 100 person-year
*HR for Febuxostat vs. Allopurinol

Kaplan-Meier Plot of CV Death



Subjects at risk

Febuxostat	3098	2815	2535	2146	1888	1626	1410	1199	992	794	593	440	230	51	0
Allopurinol	3092	2804	2510	2119	1848	1589	1397	1165	962	797	609	434	235	57	0

Secondary CV Analyses

	Febuxostat N=3098	Allopurinol N=3092	Hazard Ratio* (95% CI)
APTC	296	271	1.09 (0.92, 1.28)
All-Cause Death (On-Study)	243	199	1.22 (1.01, 1.47)
CV Death	134	100	1.34 (1.03, 1.73)
Non-CV Death	109	99	1.10 (0.84, 1.45)
All-Cause Death (On-Treatment + 30 days)	92	72	1.26 (0.93, 1.72)
CV Death	62	41	1.49 (1.01, 2.22)
Non-CV Death	30	31	0.96 (0.58, 1.58)

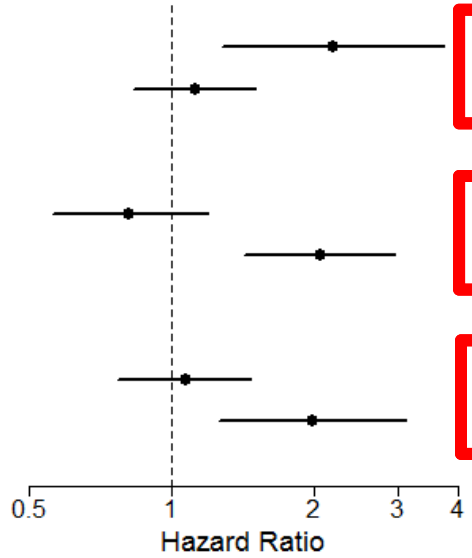
*HR for Febuxostat vs. Allopurinol

CV Death after Treatment Discontinuation

	CV Death	
	Febuxostat	Allopurinol
On-Study	134	100
On-Treatment	23	14
After Treatment (days)		
1-30	39	27
31-60	14	12
61-90	8	11
91-180	23	21
181-360	4	5
361-720	11	4
721+	12	6

Subgroup Analysis of CV Death

Subgroup	Febuxostat Events/N (%)	Allopurinol Events/N (%)	HR (95% CI)
Use of NSAIDs			
Yes	41/856 (4.8)	20/908 (2.2)	2.19 (1.28, 3.74)
No	93/2242 (4.1)	80/2184 (3.7)	1.12 (0.83, 1.50)
Low Dose Aspirin			
Yes	49/1496 (3.3)	57/1481 (3.8)	0.81 (0.56, 1.19)
No	85/1602 (5.3)	43/1611 (2.7)	2.05 (1.42, 2.95)
Any Dose Aspirin			
Yes	76/1894 (4.0)	72/1933 (3.7)	1.07 (0.77, 1.47)
No	58/1204 (4.8)	28/1159 (2.4)	1.98 (1.26, 3.11)

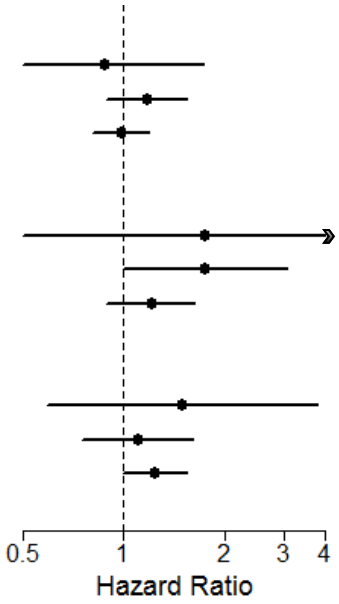


Events/N (%) = event rate (%)

Allopurinol Worse **Febuxostat Worse**

Subgroup Analysis – Baseline Renal Status

Subgroup	Febuxostat Events/N (%)	Allopurinol Events/N (%)	HR (95% CI)
MACE			
Normal	17/239 (7.1)	17/228 (7.5)	0.88 (0.45, 1.73)
Mildly Impaired	110/1217 (9.0)	92/1231 (7.5)	1.18 (0.89, 1.55)
Moderately Impaired	207/1636 (12.7)	212/1631 (13.0)	0.98 (0.81, 1.19)
CV Death			
Normal	6/239 (2.5)	3/228 (1.3)	1.75 (0.44, 7.00)
Mildly Impaired	34/1217 (2.8)	19/1231 (1.5)	1.75 (1.00, 3.08)
Moderately Impaired	93/1636 (5.7)	78/1631 (4.8)	1.21 (0.89, 1.63)
All-Cause Death			
Normal	12/239 (5.0)	7/228 (3.1)	1.49 (0.59, 3.80)
Mildly Impaired	55/1217 (4.5)	49/1231 (4.0)	1.10 (0.75, 1.61)
Moderately Impaired	175/1636 (10.7)	143/1631 (8.8)	1.24 (1.00, 1.55)



Events/N (%) = event rate (%)

Allopurinol Worse **Febuxostat Worse**

Outline

- Trial Objective and Design
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- **Summary**

Summary

- CARES was designed to rule out a hazard ratio margin of MACE > 1.3
- The Cox proportional hazards model estimated a hazard ratio of MACE associated with febuxostat of 1.03 with a 95% confidence interval of (0.89, 1.21)
- The upper bound of the 95% CI ruled out the risk margin of 1.3
- Observed increased risk of CV death associated with febuxostat


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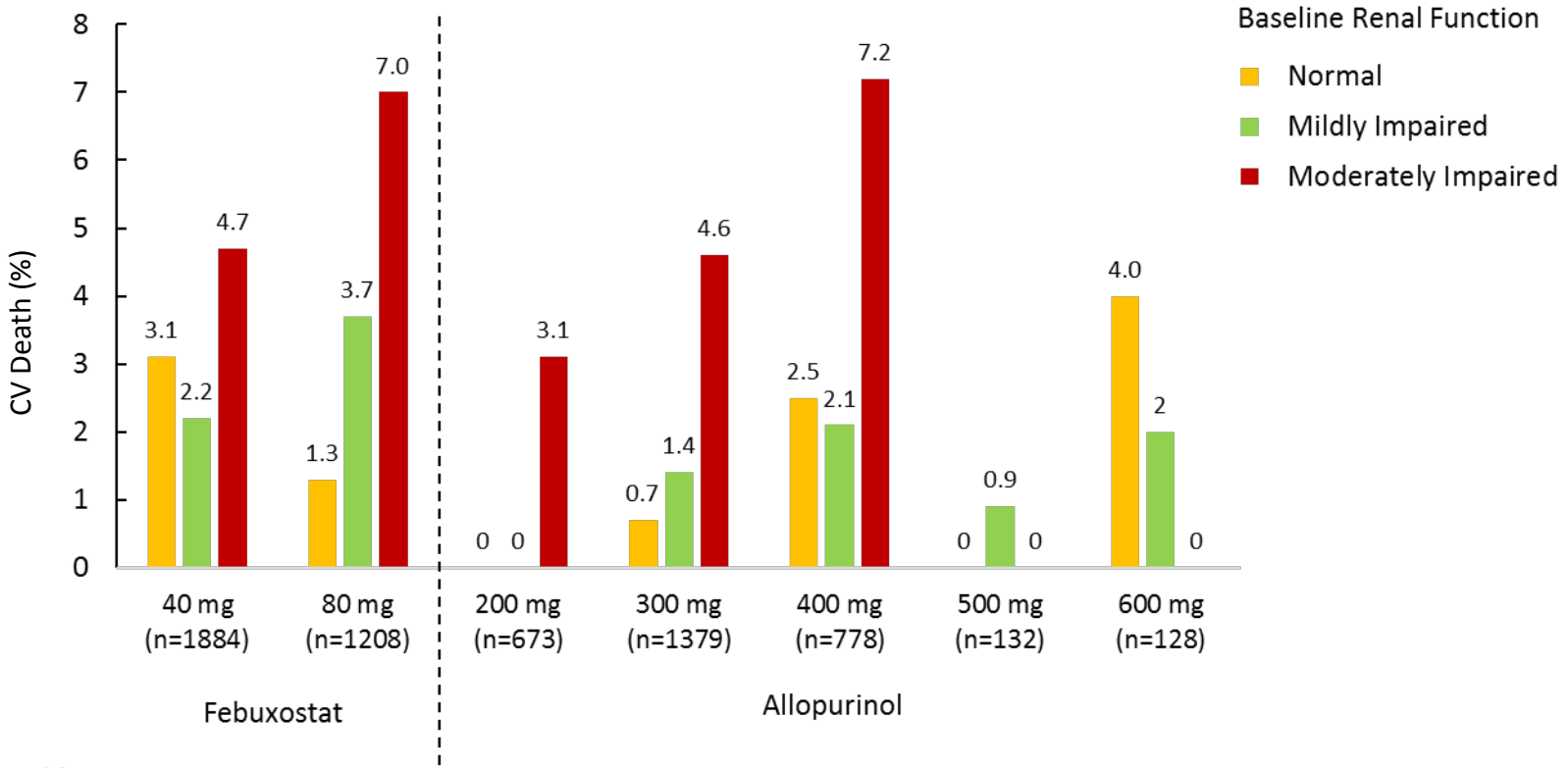
Back-up Slide Shown

CV Death by Baseline Renal Function and Final Dose



Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Joint Meeting

sNDA 21856: Febuxostat for the chronic management of hyperuricemia in patients with gout

Characteristics of Febuxostat and Allopurinol Users in Real World Settings and Utilization Patterns

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January 11, 2019

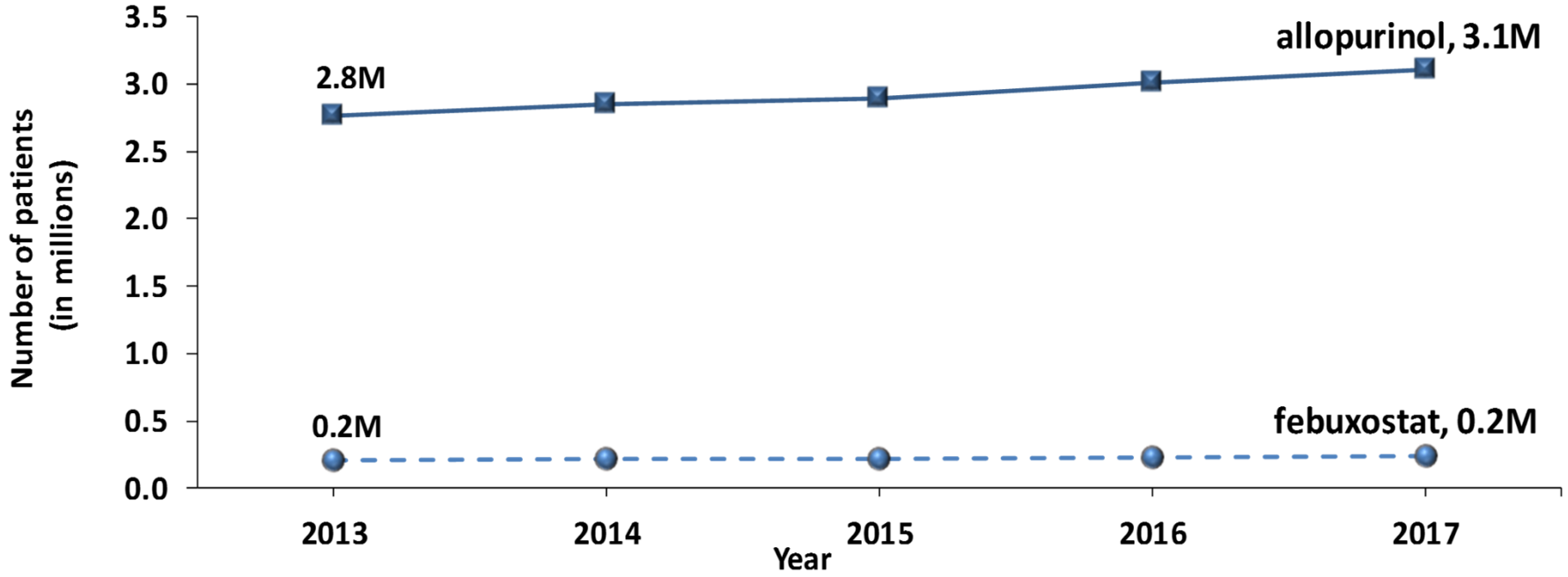
Overview

- Nationally estimated patient-level and prescription-level data
  - High-level urate lowering therapy (ULT) utilization patterns in the US
- Sentinel analyses
  - Characteristics of febuxostat and allopurinol users
  - Utilization
  - Switching

Drug Utilization: National Estimates

Patient Data: Febuxostat and Allopurinol

Nationally Estimated Number of Patients Dispensed a Prescription for Febuxostat or Allopurinol from U.S. Outpatient Retail Pharmacies

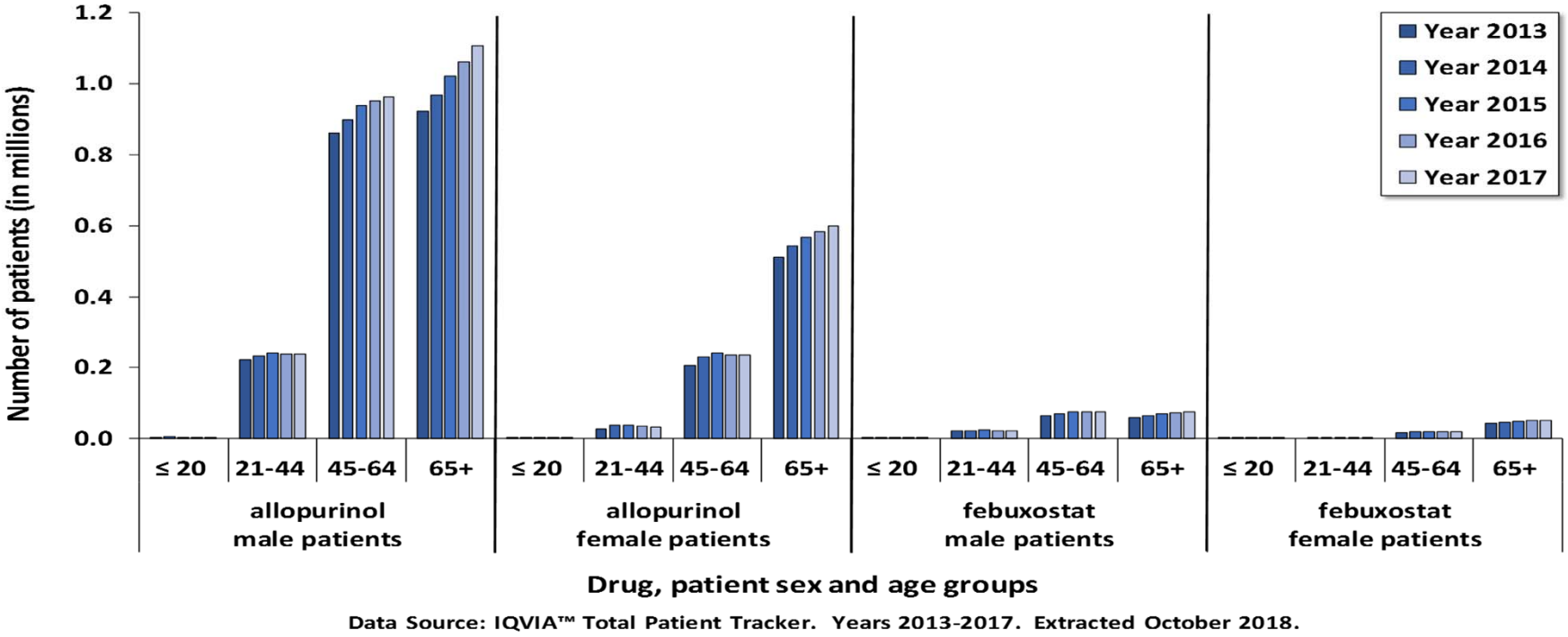


Data Source: IQVIA™ Total Patient Tracker. Years 2013-2017. Extracted October 2018.

- Allopurinol was the most widely used ULT with over 3 million patients in 2017

Patient Data by Age and Sex

Nationally Estimated Number of Patients Dispensed a Prescription for Febuxostat or Allopurinol by Patient Sex and Age Groups from U.S. Outpatient Retail Pharmacies, 2013-2017

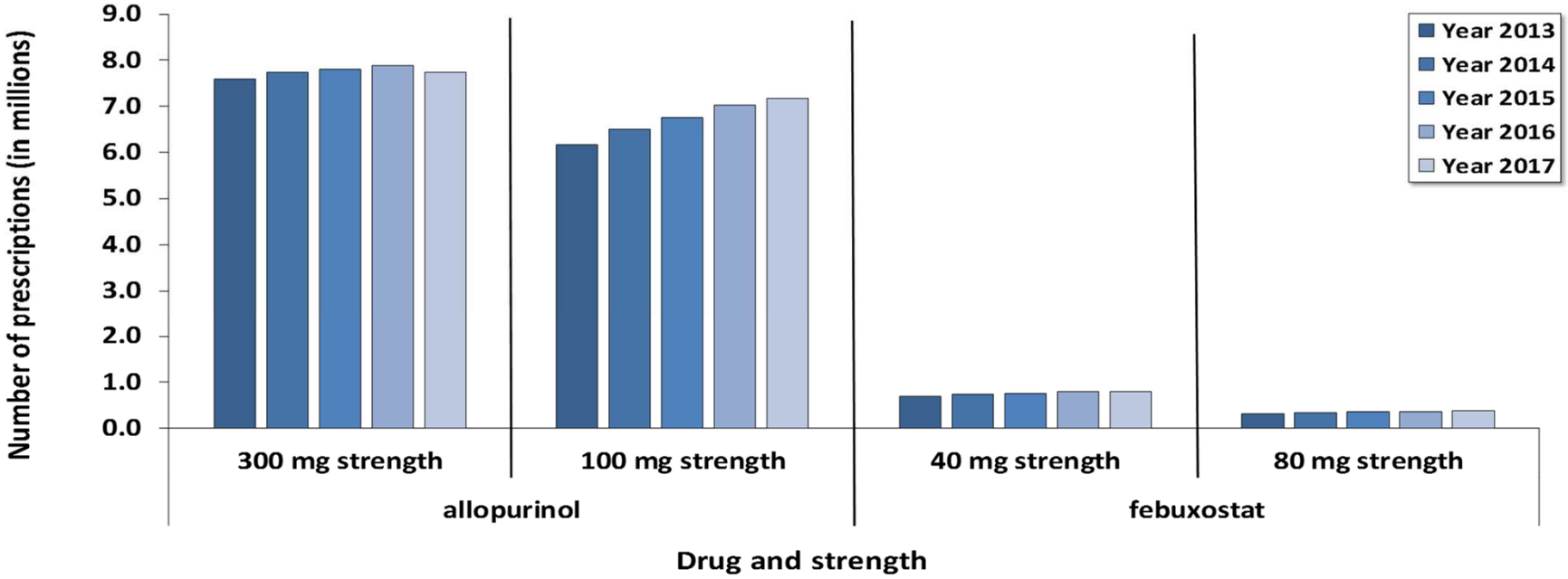


Data Source: IQVIA™ Total Patient Tracker. Years 2013-2017. Extracted October 2018.

- Males and patients aged 65 years + accounted for largest amount of allopurinol and febuxostat use

Dispensed Prescription Data by Drug Strength

Nationally Estimated Number of Prescriptions Dispensed for Febuxostat or Allopurinol from U.S. Outpatient Retail Pharmacies, by Drug Strength, 2013-2017



Data Source: IQVIA™ National Prescription Audit. Years 2013-2017. Extracted October 2018.

Note: allopurinol 500 mg strength (IV injectable) was not included in the figure above due to the negligible amount of use observed in the outpatient retail setting.

- The most commonly dispensed strengths were allopurinol 300 mg tablets and febuxostat 40 mg tablets

Sentinel Analyses

Background

- CARES trial included a select population of gout patients enriched for CVD
- Concerns about generalizability of CARES trial findings to gout patients in real world settings
- We conducted analyses in the Sentinel Distributed Database (SDD) to examine if patients in the CARES trial truly reflect gout patients in real world settings and to examine utilization of ULT

Sentinel System

- Distributed network of data partners (DPs)
- Primarily commercial insurance claims data
- Each DP contributes medical encounter and pharmacy transaction data, including inpatient and outpatient diagnoses and procedure codes and outpatient drug dispensing data
- Each DP maintains operational control over their data formatted in common data model
- Customized modular programs compatible with the common data model (Active Risk Identification Analysis (ARIA) system) are run on the distributed database

Methods

- Data from SDD from January 1, 2009 to September 30, 2016
  - 17 health plans, over 122 million enrollees

1. Characteristics of the gout population
2. Characteristics, duration of use and switching patterns among initiators of febuxostat and allopurinol
3. Comparison with CARES population

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Results

Characteristics of the Gout Population

	Patients with at least one gout diagnosis code	
	N/Mean	%/Std Dev[2]
Number of unique patients	5,031,941	
Demographics		
Age (Mean &SD)	67.8	12.2
Age: 21-44	393,716	7.8%
Age: 45-64	1,329,986	26.4%
Age: 65+	3,308,239	65.7%
Gender (Female)	1,881,665	37.4%
Gender (Male)	3,150,130	62.6%
Ever use of ULT following gout diagnosis		
Febuxostat	217,114	4.3%
Allopurinol	2,336,478	46.4%
Probenecid	85,732	1.7%
Pegloticase	144	0.0%

- Mean age of gout patients was 67 years
- More males than females were diagnosed
- Allopurinol was the most commonly used ULT following a gout diagnosis, febuxostat use appeared rare in comparison

Characteristics of Febuxostat and Allopurinol Initiators

	Febuxostat initiators		Allopurinol initiators	
	N/Mean	**%/Std Dev[2]**	**N/Mean**	**%/Std Dev[2]**
Number of unique patients	80,083		1,049,462	
Mean Age	68.3	11.9	67.3	12.1
Age: 21-44	6,503	8.1%	88,682	8.5%
Age: 45-64	20,722	25.9%	286,874	27.3%
Age: 65+	52,858	66.0%	673,906	64.2%
Gender (Female)	29,120	36.4%	359,524	34.3%
Gender (Male)	50,961	63.6%	689,900	65.7%

- Febuxostat initiators were slightly older than allopurinol initiators and had a higher proportion of females

Characteristics of Febuxostat and Allopurinol Initiators by Strength

	Patients initiating febuxostat (40mg)		Patients initiating febuxostat (80mg)		Patients initiating allopurinol (100mg)		Patients initiating allopurinol (300mg)	
	N	%/Std Dev[2]	N	%/Std Dev[2]	N	%/Std Dev[2]	N	%/Std Dev[2]
Number of patients	66,682		14,657		681,171		406,323	
Mean Age	69	11.8	65	11.8	68.7	12.3	64.9	11.6
Age: 21-44	5,041	7.6%	1,595	10.9%	51,313	7.5%	41,978	10.3%
Age: 45-64	16,447	24.7%	4,679	31.9%	169,497	24.9%	129,899	32.0%
Age: 65+	45,194	67.8%	8,383	57.2%	460,361	67.6%	234,446	57.7%
Gender (Female)	25,485	38.2%	3,990	27.2%	260,528	38.2%	109,323	26.9%
Gender (Male)	41,195	61.8%	10,667	72.8%	420,621	61.7%	296,982	73.1%

- The mean age of new initiators was similar across ULTs ranging from 65-69 years
- A higher proportion of allopurinol 300 mg and febuxostat 80 mg initiators were male compared to febuxostat 40 mg and allopurinol 100 mg

CVD History, Gout Severity and CKD in Febuxostat and Allopurinol Initiators

	Febuxostat initiators		Allopurinol initiators	
	N/Mean	**%/Std Dev[2]**	**N/Mean**	**%/Std Dev[2]**
Baseline cardiovascular history				
Myocardial infarction	1,204	1.5%	15,897	1.5%
Unstable angina	1,267	1.6%	16,017	1.5%
Stroke	2,197	2.7%	30,870	2.9%
Transient ischemic attack	570	0.7%	7,984	0.8%
Perpheral vascular disease	3,288	4.1%	40,445	3.9%
Diabetic macro- or microvascular disease	6,926	8.6%	80,595	7.7%
Baseline gout severity measures				
Tophi	11,816	14.8%	90,446	8.6%
Gouty arthritis	46,593	58.2%	481,661	45.9%
Kidney stones	8,527	10.6%	92,022	8.8%
Gout flares	61,655	77.0%	719,277	68.5%
Tophi and gouty arthritis	9,226	11.5%	57,979	5.5%
Tophi and kidney stones	1,462	1.8%	9,414	0.9%
Gouty arthritis and kidney stones	5,149	6.4%	42,766	4.1%
Tophi and gouty arthritis and kidney stones	1,169	1.5%	5,982	0.6%
Chronic kidney disease	10,958	13.7%	111,424	10.6%

- CVD at baseline was similar between febuxostat and allopurinol initiators
- Febuxostat users tended to have more severe gout than allopurinol initiators
- Febuxostat users were more likely to have CKD

Duration of Use Among Febuxostat and Allopurinol Initiators

	<1 month	1 - <3 months	3 - <6 months	6 months - <1 year	1 - <3 years	3 - <5 years	5+ years	Median (IQR)
Exposures	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**(days)**
Febuxostat 40 mg (n=66,682)	3.5	34.4	15	15.2	23.2	6.8	1.9	165 (436)
Febuxostat 80 mg (n=14,657)	2.9	32.8	16.2	17.3	23.8	5.7	1.3	180 (400)
Febuxostat any strength (n=80,083)	3.2	29.6	14.1	15.7	26.7	8.3	2.4	210 (538)
Allopurinol 100 mg (n=681,171)	4.4	27.4	14.2	15.4	26.1	9.2	3.3	216 (562)
Allopurinol 300 mg (n=406,322)	2.6	26	13.1	15.2	28	10.8	4.3	270 (655)
Allopurinol any strength (n=1,049,461)	2.8	21.9	12.4	15.1	30.4	12.4	5	334 (505)

- Around 30% of febuxostat and 22% allopurinol initiators continued use for 1-3 months
- Very small proportions of ULT initiators continued use long term beyond 5 years
- Allopurinol initiators had longer median durations of use compared to febuxostat initiators

Top Ten Switching Patterns

Switching scenarios	New Users Switched (%)	Females (%)	Males (%)	21-44 years	45-64 years	65+ years
Allopurinol (100mg) users that Switch to Allopurinol (300mg)	13.4	10.6	15.2	16.2	15.2	12.3
Febuxostat users (any strength) that Switch to Allopurinol (any strength)	9.7	10.1	9.5	8.0	8.8	10.2
Febuxostat (40mg) users that Switch to Febuxostat (80mg)	9.1	7.5	10.1	10.3	10.1	8.6
Allopurinol (300mg) users that Switch to Allopurinol (100mg)	6.8	7.9	6.4	6.2	5.8	7.4
Febuxostat (40mg) users that Switch to Allopurinol (100mg)	6.3	7.3	5.6	3.8	5.0	7.0
Febuxostat (80mg) users that Switch to Febuxostat (40mg)	5.1	6.9	4.5	2.6	4.5	5.9
Febuxostat (80mg) users Switch to Allopurinol (300mg)	4.2	3.9	4.3	4.3	4.1	4.1
Febuxostat (40mg) users that Switch to Allopurinol (300mg)	3.5	2.9	3.9	4.2	3.8	3.3
Febuxostat (80mg) users s that Switch to Allopurinol (100mg)	3.3	3.9	3.1	2.0	2.8	3.9
Allopurinol users (any strength) that Switch to Febuxostat (any strength)	2.7	3.0	2.5	1.9	2.3	2.9

- The proportion of new users that switched between ULTs during follow-up was low (generally < 10%)
- The largest proportion of new user switches occurred from allopurinol 100 mg to 300 mg and febuxostat 40 mg to febuxostat 80 mg

Duration of Use Before Switching

	<1 month	1 - <3 months	3 - <6 months	6 months - <1 year	1 - <3 years	3 - <5 years	5+ years	Median time to switch (IQR)
Exposures	%	%	%	%	%	%	%	(days)
Febuxostat (any strength), switch to Allopurinol (any strength) (n=19,363)	**11.7**	**37.3**	**15.1**	**14.2**	**17.7**	**3.5**	**0.5**	**95 (278)**
Febuxostat 40 mg, switch to Febuxostat 80 mg (n= 9,598)	9.4	36.2	20	16.1	15.4	2.5	0.3	108 (221)
Febuxostat 40 mg, switch to Allopurinol 100 mg (n=11,354)	12.6	41.5	15	13.1	14.8	2.6	0.4	90 (214)
Febuxostat 80 mg, switch to Febuxostat 40 mg (n=1,994)	6.6	29.1	18	17.5	23.5	4.5	0.9	173 (373)
Allopurinol (any strength), switch to Febuxostat (any strength) (n=56,401)	**9.3**	**31.4**	**17.1**	**16.3**	**20.2**	**4.7**	**1**	**134 (325)**
Allopurinol 100 mg, switch to Allopurinol 300 mg (n=145,823)	15.2	32.1	18.2	15.3	15.5	3	0.5	100 (240)
Allopurinol 100 mg, switch to Febuxostat 40 mg (n= 32,022)	11.8	37.4	17.4	14.9	15.1	30	92	93 (240)
Allopurinol 300 mg, switch to Allopurinol 100 mg (n= 63,279)	12.7	25.9	14.5	15.7	23.3	31	97	165 (424)

- Median time to switch was longer among switchers from allopurinol to febuxostat (134 days) than from febuxostat to allopurinol (95 days)
- Approximately 40% of febuxostat users and 30% of allopurinol users switched after 1-3 months

Discussion

Comparison with CARES Trial

Comparison of demographics and clinical characteristics among CARES and SDD patients

	CARES		SDD	
	Febuxostat	Allopurinol	Febuxostat	Allopurinol
Aged 65 years+ (%)	48.9	51.3	66	64.2
Male (%)	84.1	83.8	62.6	65.1
History of MI (%)	38.6	39.8	1.5	1.5
History of stroke (%)	14.8	13.3	2.7	2.9
Median duration of use (days)	728	719	210	334

ULT users in the CARES trial were:

1. Younger than in real-world settings
2. More males than in real-world settings
3. Higher prevalence of both CVD and CKD than real-world settings

Summary-ULT Utilization in Real World Settings

- Allopurinol: most commonly used ULT – 100 mg strength
- Febuxostat use comparatively rare (4.3%)
- Few ULT initiators continued use long term (beyond 5+ years)
- Majority remained ULT for 1-3 months only
- Allopurinol users tended to have better adherence

Summary-ULT switching in Real World Settings

- Proportion of new ULT users that switched was low
- Largest proportion (13.4%) switches from allopurinol 100 mg to 300 mg
- Most patients switched after 1-3 months

Conclusions

- Important differences in characteristics of ULT initiators in SDD compared to CARES trial
- In Real World settings ULT initiators were older and less likely to have recent CVD or CKD
- Adherence was poorer in the real-world settings and switching between ULTs was low
- Differences need to be considered in interpreting the results of the CARES study

Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Joint Meeting

sNDA 21856: Febuxostat for the chronic management of hyperuricemia in patients with gout

FDA Charge to the Committees

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January 11, 2019

Summary of CARES Trial Results

	Febuxostat N=3098 PY=8799.5	**Allopurinol** N=3092 PY=8675.7	**Hazard Ratio*** **(95% CI)**
MACE	**335** [3.8]	**321** [3.7]	**1.03 (0.89, 1.21)**
CV Death	134	100	1.34 (1.03, 1.73)
Non-fatal MI	111	118	0.93 (0.72, 1.21)
Non-fatal Stroke	71	70	1.01 (0.73, 1.41)
Unstable Angina with Urgent Coronary Revascularization	49	56	0.86 (0.59, 1.26)

PY=person-year
[ ]: incidence rate per 100 person-year
*HR for Febuxostat vs. Allopurinol

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Therapeutic Armamentarium in Gout

Product	Approved Dosing	Efficacy and Safety
First Line Therapy: Xanthine Oxidase Inhibitors (XOI)		
Allopurinol LASSO Study Febuxostat NDA at Drugs@FDA	100-800 mg/d; Doses >300 mg/d divide into twice daily (BID) administration	• 300 mg dose ~ 2 to 3.5 mg/dL* mean ↓sUA • Hypersensitivity reactions, cutaneous reactions, gastrointestinal intolerance
Febuxostat Febuxostat NDA at Drugs@FDA	40-80 mg daily (QD)	• 80 mg dose ~ 4.5 mg/dL* mean ↓sUA • CV risk, hepatoxicity, cutaneous reactions
Second Line Therapy: Uricosuric Agents		
Probenecid Pui et al, J Rheum 2013	500-1000 mg BID ($T_{1/2}$ 3-8 hrs)	• Mean 1.3 g/d dose ~ 2.9 mg/dL* mean ↓sUA • Nephrolithiasis
Lesinurad Zurampic NDA at Drugs@FDA	200 mg QD with concomitant XOI	• 200 mg dose ↓sUA on background XOI ~ 1 mg/dL mean • Renal events including failure, CV risk
Lesinurad/Allopurinol FDC Duzallo NDA at Drugs@FDS	LES200mg/ALLO200 mg QD or LES200mg/ALLO300 mg QD	• Same safety issues as with lesinurad and allopurinol
Third Line Therapy: Uricase		
Pegloticase Krystexxa NDA at Drugs@FDA	8 mg every 2 weeks intravenously (IV)	• Mean ↓sUA ~6.6 to 6.8* mg/dL • Anaphylaxis, infusion reactions, ↑CHF

Regulatory Actions for AC Discussion

- Strengthening current CV warning
- Add boxed warning for CV death
- Change indication to second line therapy
- Citizens Petition request to withdraw febuxostat from the market

Discussion Points

1. **DISCUSSION:** Discuss the results of the "Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)" study, particularly major adverse cardiovascular events (MACE) and cardiovascular (CV) mortality. Please consider the following in your discussion:
    a. Biological plausibility of CV mortality
    b. Strength of the findings for CV mortality, considering the totality of available data.

Discussion Points

2. **DISCUSSION:** Discuss the benefits of febuxostat for the treatment of hyperuricemia in patients with gout.
3. **DISCUSSION:** Given the results of the CARES study, discuss whether the benefit-risk profile of febuxostat for the treatment of hyperuricemia in patients with gout has changed. Address the following in your discussion:
    a. Discuss any patient populations in which the benefits outweigh the risks of the use of febuxostat
    b. Discuss any patient populations in which the benefits do not outweigh the risks of the use of febuxostat.

Discussion Points

4. **DISCUSSION:** Discuss the following potential regulatory activities in response to the results of the CARES study and the potential clinical impact of these options.
    a. Update existing warning regarding Cardiovascular Events in the febuxostat product label
    b. Addition of a boxed warning to the febuxostat product label
    c. Modify labeling to limit use of febuxostat to second line therapy (e.g. 2nd line therapy in patients who have failed allopurinol)
    d. Withdrawal of febuxostat from the market.

Voting Question

5. **VOTING:** Based upon the available data, is there a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout? (Yes/No)
    - If you voted "Yes", describe the patient population with a favorable benefit-risk profile for use of febuxostat. Also, describe any other recommendations (e.g. labeling changes) you may have for use of febuxostat in this population
    - If you voted "No", discuss your rationale, the impact of this recommendation, and any other recommendations you may have.


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