CARDIOVASCULAR SAFETY OF FEBUXOSTAT OR ALLOPURINOL IN PATIENTS WITH GOUT AND CARDIOVASCULAR DISEASE (The CARES Trial)

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Objectives and Endpoints of CARES

- **Primary objective**: To demonstrate that major CV event rates with febuxostat are noninferior to allopurinol in patients with gout with CV disease
  - **Primary endpoint**: Composite of first occurrence of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization for unstable angina
  - **Secondary endpoints**: Evaluation of time from randomization to the first occurrence of MACE:
    - Composite of CV death, nonfatal MI, nonfatal stroke
    - Other secondary endpoints: individual rates of CV death, nonfatal MI, or nonfatal stroke
    - Other endpoint: All-cause mortality

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Study Design

- Randomized, double-blind, multicenter controlled study of febuxostat versus allopurinol in patients with gout and cardiovascular disease in the USA, Canada, and Mexico

*At randomization, patients were stratified according to renal function. After randomization, dose titration of allopurinol was made on the basis of renal function. Febuxostat did not require dose adjustment by renal function.

Disposition of Patients

6190 patients randomized and received 1 dose of study drug
(modified ITT population)

Febuxostat
N=3098

1397 (45.0%)
Discontinued study visits early

191 (6.2%) – adverse events (includes death)
595 (19.2%) – unwillingness to continue
52 (1.7%) – major protocol deviation
226 (7.3%) – lost to follow-up
333 (10.7%) – other reason

Allopurinol
N=3092

1391 (44.9%)
Discontinued study visits early

172 (5.6%) – adverse events (includes death)
587 (19.0%) – unwillingness to continue
46 (1.5%) – major protocol deviation
223 (7.2%) – lost to follow-up
363 (11.7%) – other reason

ITT, intention-to-treat.
Time to Primary Endpoint (CV Death, Nonfatal MI, Nonfatal Stroke, Urgent Revascularization for UA)

Modified ITT population; hazard ratio 1.03 (*one-sided repeated CI bound, 1.23)

Events, n (%)
- Allopurinol: 321 (10.4)
- Febuxostat: 335 (10.8)

Cumulative incidence of the primary endpoint (%)

Number of subjects at risk
- Febuxostat (n): 3092 2764 2465 2080 1815 1560 1361 1132 933 767 589 437 258
- Allopurinol (n): 3098 2784 2493 2111 1854 1589 1369 1165 955 778 573 441 264

*Using alpha=0.015.

CI, confidence interval; CV, cardiovascular; ITT, intention-to-treat; MI, myocardial infarction; UA, unstable angina.
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Febuxostat (N=3098)</th>
<th>Allopurinol (N=3092)</th>
<th>Hazard ratio for febuxostat group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of CV death, nonfatal MI, or nonfatal stroke</td>
<td>296 (9.6)</td>
<td>271 (8.8)</td>
<td>1.09 (0.92, 1.28)</td>
</tr>
<tr>
<td>CV death</td>
<td>134 (4.3)</td>
<td>100 (3.2)</td>
<td>1.34 (1.03, 1.73)*</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>111 (3.6)</td>
<td>118 (3.8)</td>
<td>0.93 (0.72, 1.21)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>71 (2.3)</td>
<td>70 (2.3)</td>
<td>1.01 (0.73, 1.41)</td>
</tr>
<tr>
<td>Urgent revascularization due to unstable angina</td>
<td>49 (1.6)</td>
<td>56 (1.8)</td>
<td>0.86 (0.59, 1.26)</td>
</tr>
</tbody>
</table>

*P=0.034.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
Mortality Endpoints

Cardiovascular Mortality

Modified ITT; hazard ratio 1.34 (95% CI 1.03, 1.73)

Events, n (%)
Febuxostat, 134 (4.3)
Allopurinol, 100 (3.2)

Events, n (%)
Febuxostat, 243 (7.8)
Allopurinol, 199 (6.4)

Cumulative incidence of cardiovascular mortality (%)

Number of subjects at risk
Febuxostat (n): 3098 2823 2550 2174 1922 1659 1440 1243 1033 838 627 482 288
Allopurinol (n): 3092 2807 2530 2152 1898 1637 1433 1204 1008 838 646 489 287

CI, confidence interval; ITT, intent-to-treat.

All-Cause Mortality

Modified ITT; hazard ratio 1.22 (95% CI 1.01, 1.47)

Events of adjudicated sudden cardiac death
Febuxostat, 83 (2.7%)
Allopurinol, 56 (1.8%)

Events, n (%)
Febuxostat, 243 (7.8)
Allopurinol, 199 (6.4)

Cumulative incidence of all-cause mortality (%)

Number of subjects at risk
Febuxostat (n): 3098 2828 2552 2179 1928 1666 1447 1251 1038 840 631 487 289
Allopurinol (n): 3092 2812 2540 2161 1906 1648 1444 1215 1015 842 650 489 288

CI, confidence interval; ITT, intent-to-treat.
## On-Treatment Analysis*

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<tr>
<th>Number (%)</th>
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<th>Allopurinol (N=3092)</th>
<th>Hazard ratio for febuxostat group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>242 (7.8)</td>
<td>238 (7.7)</td>
<td>1.00 (0.82, 1.22)**</td>
</tr>
<tr>
<td>CV death</td>
<td>62 (2.0)</td>
<td>41 (1.3)</td>
<td>1.49 (1.01, 2.22)†</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>93 (3.0)</td>
<td>106 (3.4)</td>
<td>0.87 (0.66, 1.34)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>59 (1.9)</td>
<td>62 (2.0)</td>
<td>0.94 (0.66, 1.34)</td>
</tr>
<tr>
<td>Urgent revascularization due to unstable angina</td>
<td>45 (1.5)</td>
<td>44 (1.4)</td>
<td>1.00 (0.66, 1.52)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>92 (3.0)</td>
<td>72 (2.3)</td>
<td>1.26 (0.93, 1.72)</td>
</tr>
</tbody>
</table>

*Prespecified: On drug and up to 30 days off drug; **97.0% CI; †P=0.047.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
Summary

• Rates of major adverse CV events on febuxostat were noninferior to allopurinol in patients with gout and CV disease

• All-cause mortality was greater on febuxostat versus allopurinol due to an imbalance in CV deaths, particularly sudden cardiac death

• These observations occurred in the following context:
  – Urate lowering on febuxostat was greater than allopurinol
  – Similar gout flare rates between groups during the trial
  – No differences between groups for serum potassium, lipids, glucose, creatinine, or blood pressure
  – No preclinical signals for cardiac toxicity observed with febuxostat
  – No differences in the rates of major nonfatal cardiovascular events

CV, cardiovascular.
Summary (2)

- There was a high rate of study discontinuation (45%).
- Rates of withdrawal were similar in the febuxostat and allopurinol groups.
- Sensitivity analysis (on treatment plus 30 days within discontinuation of study drug) showed:
  - Similar rates of the primary endpoint on febuxostat and allopurinol, comparable with the modified ITT analysis.
  - Higher rates of all-cause and CV death on febuxostat versus allopurinol were also comparable with the modified ITT analysis.
  - The majority of deaths occurred off drug.
- Further safety analyses from the trial are ongoing to evaluate the unexpected mortality findings in CARES.

CV, cardiovascular; ITT, intent-to-treat.