

Long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with gout: a multicentre, prospective, randomised, open-label, clinical trial. The Febuxostat versus Allopurinol Streamlined Trial (FAST).

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1 **Summary**

2 **Background**

3 Febuxostat and allopurinol are urate-lowering therapies used to treat patients with gout. Following
4 concerns about the cardiovascular safety of febuxostat, the European Medicines Agency (EMA)
5 recommended a post-licensing study comparing the cardiovascular (CV) safety of febuxostat versus
6 allopurinol.

7 **Methods**

8 We conducted a prospective, randomised, open-label, blinded endpoint (PROBE) non-inferiority trial
9 of febuxostat versus allopurinol in patients with gout in the UK, Denmark, and Sweden. Eligible
10 patients were 60 years or older, currently treated with allopurinol, with at least one additional
11 cardiovascular risk factor. After increasing allopurinol dose if necessary to achieve serum urate
12 levels < 0.357 mmol/L (< 6 mg/dL), patients were randomly assigned to continue allopurinol (at
13 optimised dose) or start febuxostat at a dose of 80mg daily, increasing to 120mg, if necessary, to
14 achieve serum uric acid level < 0.357 mmol/L. The primary outcome was the composite of
15 hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome,
16 non-fatal stroke or cardiovascular death. The hazard ratio (febuxostat versus allopurinol) in a Cox
17 proportional hazards model was assessed for non-inferiority (limit of 1.3) in an on-treatment (OT)
18 analysis and then by intention to treat (ITT). This study is registered with the EU Clinical Trials
19 Register (EudraCT 2011-001883-23) and ISRCTN (ISRCTN72443728).

20 **Findings**

21 From 20 December, 2011, to 26 January, 2018, 6128 patients (mean age 71, 85.3% male, 33.4% prior
22 CV disease) were enrolled and randomised to receive allopurinol (n=3065) or febuxostat (n=3063))
23 and were followed up to December 2019, during which 5.5% and 6.2% respectively withdrew from
24 all follow up. Median follow-up time in the study was 1467 days [IQR 1029-2052] and median on-

25 treatment follow-up period was 1324 days [IQR 870-1919]. In both the on-treatment and intention-
26 to-treat analyses, febuxostat therapy was non-inferior to allopurinol therapy for incidence of the
27 primary endpoint (OT analysis: febuxostat 172 patients [1.72 events per 100 patient years];
28 allopurinol 241 patients [2.05 events per 100 patient years]; hazard ratio 0.85 [95% CI 0.70-1.03],
29 $p < 0.001$; ITT analysis: febuxostat 256 patients [2.05 events per 100 patient years], allopurinol 285
30 patients [2.29 events per 100 patient years]; hazard ratio 0.89 [95% CI 0.75-1.06], $p < 0.001$). A total
31 of 222 (7.2%) patients died and 1720 (57.3%) experienced at least one serious adverse event (SAE) in
32 the febuxostat group compared to 263 deaths (8.6%) and 1812 patients with one or more SAE
33 (59.4%) in the allopurinol group. In the febuxostat group, 973 patients [32.4%] discontinued
34 randomised therapy compared with 503 patients [16.5%] on allopurinol.

35 **Interpretation**

36 Febuxostat was non-inferior to allopurinol therapy for the primary cardiovascular outcome. Long-
37 term use of febuxostat was not associated with an increased risk of death or serious adverse events
38 compared with allopurinol.

39 **Funding:** Menarini funded the study. Menarini received support from Ipsen and Teijin Pharma
40 Limited. The University of Dundee was the sponsor and the funder had no involvement in the
41 running of the study.

42

43 **Research in context**

44

45 **Evidence before this study**

46 We searched PubMed on 17 September, 2020, using the search terms “febuxostat”, “allopurinol”,
47 and “cardiovascular outcomes”. We searched for original articles with no date or language
48 restriction for any randomised clinical trials with >500 participants comparing febuxostat with
49 allopurinol in terms of cardiovascular outcomes. We found one trial, the ‘Cardiovascular Safety of
50 Febuxostat or Allopurinol in Patients with Gout (CARES)’ trial. This trial, involving 6190 randomised
51 patients with gout and major cardiovascular coexisting conditions, reported that febuxostat was
52 non-inferior to allopurinol with respect to rates of adverse cardiovascular events. However, the risk
53 of death from any cause (febuxostat n=243 (7.8%), allopurinol n=199 (6.4%); HR 1.22 (95% CI 1.01-
54 1.47); p=0.04) and the risk of cardiovascular death (febuxostat n=134 (4.3%), allopurinol n=100
55 (3.2%); HR 1.34 (95% CI 1.03-1.73); p=0.03) (modified intention to treat analysis) were higher in the
56 febuxostat group than in the allopurinol group in CARES.

57 **Added value of this study**

58 The FAST study was a large, multicentre, prospective, randomised, open-label, blinded endpoint
59 non-inferiority study to compare the cardiovascular safety of febuxostat versus allopurinol in 6128
60 patients with gout and at least one additional cardiovascular risk factor, who were already treated
61 with allopurinol. The population studied differed from that in the CARES trial. FAST participants were
62 generally at lower cardiovascular risk than CARES participants as only about one third of patients in
63 FAST had prior major cardiovascular comorbidity. Daily doses of febuxostat in FAST were higher
64 (80mg or 120mg daily) than in CARES (40mg or 80 mg daily) and dose ranges of allopurinol were
65 wider in FAST (100mg-900mg daily) than CARES (200-600mg daily). Only 5.8% of patients in FAST
66 withdrew from all follow up, and randomised treatment discontinuation rates (16.5% in the

67 allopurinol group and 32.4% in the febuxostat group) were lower than in the CARES trial. In CARES,
68 45.0% of patients did not complete all trial visits and 56.6% of patients discontinued randomised
69 treatment prematurely. FAST used record-linkage to national healthcare databases to complement
70 other methods of reporting for the detection of hospitalisations and deaths. We found that
71 febuxostat was non-inferior to allopurinol for the primary composite endpoint of hospitalisation for
72 non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke or
73 cardiovascular death during a median on-treatment period of 1324 days [IQR 870, 1919] or 3.63
74 years. In contrast to CARES, treatment with febuxostat was not associated with an increase in
75 cardiovascular death or all-cause death in FAST, nor in the subgroup of patients in FAST with a
76 baseline history of MI, stroke or acute coronary syndrome. Overall there were fewer deaths in the
77 febuxostat group (62 CV deaths and 108 all-cause deaths (OT), 117 CV deaths and 222 all-cause
78 deaths (ITT)), than in the allopurinol group (82 CV deaths and 174 all-cause deaths (OT), 122 CV
79 deaths and 263 all-cause deaths (ITT)).

80 **Implications of all the available evidence**

81 Whilst the CARES study suggested that febuxostat therapy may be associated with higher risk of all-
82 cause mortality and cardiovascular mortality than allopurinol, the FAST study, with better
83 ascertainment of events, found no increase in these risks.

84

85

86 **Introduction**

87 Gout is a metabolic disorder in which prolonged elevation of serum urate can lead to the deposition
88 of crystals of monosodium urate (MSU), tophus formation, chronic inflammatory arthritis,
89 urolithiasis, and nephropathy, as well as to recurrent flares of acute arthritis and bursitis. Gout is
90 frequently associated with co-morbidities such as chronic kidney disease, obesity, diabetes mellitus,
91 hypertension and cardiovascular disease and with increased mortality.¹⁻³ In addition to treatment of
92 acute flares with anti-inflammatory drugs, management of gout requires long term therapy with
93 urate lowering therapy (ULT) to persistently reduce the SUA below its crystallisation threshold in
94 order to dissolve crystal deposits, prevent further crystal deposition, recurrent flares of gout and
95 progressive joint damage. The most widely used urate lowering medications are the xanthine
96 oxidase inhibitors (XOI), allopurinol and febuxostat. Prophylaxis against acute flares of gout is
97 recommended when treatment is initiated with ULT or following dose increases of a XOI, typically for
98 a period of up to six months.⁴

99 Initial clinical trials comparing febuxostat to allopurinol or placebo identified a numerically higher
100 risk of cardiovascular events in patients taking febuxostat.⁵⁻⁸ Marketing authorisation for febuxostat
101 was granted after a subsequent 6-month randomised controlled trial of febuxostat compared to
102 allopurinol in 2269 participants (the CONFIRMS trial)⁹ showed equal numbers (0.4%) of adjudicated
103 cardiovascular events with febuxostat 80mg and allopurinol, and no cardiovascular deaths in the
104 febuxostat treated patients. However, because of lingering concerns about the possibility of
105 increased cardiovascular risk with febuxostat, the European Union Risk Management Plan for
106 febuxostat indicated that a post-authorisation safety study should be carried out in Europe in
107 patients with gout to evaluate the cardiovascular effects of febuxostat versus standard urate
108 lowering therapy with allopurinol. The Febuxostat versus Allopurinol Streamlined Trial (FAST) was
109 approved to fulfil this requirement.

110 **Methods**

111 **Study Design and participants**

112 A prospective, randomised, open-label, blinded endpoint (PROBE) multi-centre trial was undertaken
113 in patients with gout at 18 regional centres in three countries (UK – Scotland and England, Denmark
114 and Sweden).¹⁰ The study protocol (appendix pp157-217) was approved by ethics committees and
115 regulatory authorities in each country. All participants gave written informed consent.

116 Patients were mainly recruited from 850 primary care practices in the UK and Denmark (by search of
117 primary care records for potentially eligible patients), but also from two secondary care centres in
118 Scotland, and via two clinical research organisations in Sweden. Eligible patients were aged 60 years
119 or older, with gout,¹¹ who in the opinion of the recruiting physician required urate lowering therapy.
120 No patients with asymptomatic hyperuricaemia were recruited to the study. Eligible participants had
121 at least one additional cardiovascular risk factor (appendix p6) and were already receiving
122 allopurinol therapy. Patients with a history of myocardial infarction or stroke in the previous 6
123 months and those with congestive heart failure, New York Heart Association (NYHA) Class III or IV, or
124 severe renal impairment were excluded. A full list of inclusion and exclusion criteria is detailed in the
125 appendix (appendix pp4-5).

126 **Randomisation**

127 At the screening visit, serum urate was measured. If the SUA was not controlled to the European
128 League Against Rheumatism (EULAR) target of < 0.357 mmol/L (<6mg/dL)¹² on the patient's pre-
129 study allopurinol dose, this was increased by 100mg daily every two weeks until the urate was at
130 target or the patient reached the maximum licensed dose (900mg daily) or maximum tolerated dose
131 of allopurinol. This dose increase was carried out because febuxostat 80mg is a more potent urate
132 lowering therapy than low dose allopurinol. The dose increase was carried out every two weeks in all
133 patients who were not yet at target urate, unless there were tolerability issues, or the maximum
134 licensed dose had been reached, in which case patients could continue in the study even if the target
135 urate had not been reached. After the allopurinol dose had been optimised to reach the target urate

136 level, or immediately for patients who were already controlled to target at screening, patients were
137 randomly allocated to receive allopurinol therapy or febuxostat using a central web-based
138 randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow. The
139 randomisation system could be accessed via an interactive voice response system or by a web-based
140 application. The randomisation list was created by a statistician in the Robertson Centre based
141 on randomised permuted blocks of size four stratified according to previous cardiovascular events
142 (myocardial infarction, stroke or hospitalisation for congestive heart failure or peripheral vascular
143 disease). Randomised therapy was not blinded to participants, site staff and treating physicians but
144 was blinded to the endpoint adjudication committee.

145 Post-randomisation, while the majority of patients remained on the daily dose assigned at
146 randomisation, the daily dose of allopurinol or febuxostat could be reduced or increased by a
147 physician within the licensed daily dose limits based on clinical discretion, for example, reduced due
148 to tolerability issues or increased due to inadequate control of urate levels identified during annual
149 visits.

150 Allopurinol was chosen as the comparator for febuxostat because it is the long-established, first-line
151 ULT for gout.

152 **Procedures**

153 Allopurinol 100mg and 300mg tablets (Salutas Pharma GmbH, Barleben, Germany; Teva
154 Pharmaceutical Works Private Limited company, Debrecen, Hungary) and febuxostat 80mg and
155 120mg tablets (Patheon France, Bourgoin Jallieu, France; Menarini, Dresden, Germany) were
156 supplied directly by post to participants from the research pharmacy at the University of Dundee
157 (except in Sweden where they were supplied from the Dundee research pharmacy via a local
158 pharmacy). Allopurinol was given orally at the daily dose required to control urate levels to < 0.357
159 mmol/L or the maximum tolerated or licensed dose. Febuxostat was commenced orally at 80mg
160 daily. After two weeks, the SUA was measured in those taking febuxostat and if not controlled to $<$

161 0.357 mmol/L, the febuxostat dose was increased to 120mg daily. All patients had a washout period
162 of seven days (7-21 days) after randomisation before starting randomised therapy.

163 Six months of prophylaxis against gout flares was offered to all patients at the start of randomised
164 therapy. Prophylaxis was started earlier in any patients whose allopurinol dose was increased during
165 the allopurinol lead-in phase and was offered again at any time during the study when a patient's
166 dose of ULT was increased. First-line gout flare prophylaxis was with colchicine (0.5mg once or twice
167 daily) and second-line alternatives were non-steroidal anti-inflammatory drugs (naproxen, diclofenac
168 or meloxicam) with gastric protection (omeprazole or ranitidine). Patients could decline or
169 discontinue gout flare prophylaxis at any time. Any gout flares that occurred during the study were
170 managed at the discretion of the patient's local treating physician according to local guidelines.

171 All patients had an annual follow-up visit during which serum urate, urea, creatinine and
172 electrolytes, and liver function tests were measured. In addition, all patients had two-monthly
173 follow-up contacts with the study team. Adverse events could be reported at any time by patients or
174 health professionals. Record-linkage to centralised databases for records of hospitalisations, deaths
175 and cancers was carried out at regular intervals during the study in the UK (Public Health Scotland
176 and NHS Digital) and Denmark (Danish Health Data Board (Sundhedsdatastyrelsen)) (except for the
177 last year of study follow-up in Denmark). Although significant attempts were made by the
178 investigators to obtain similar record-linkage data in Sweden, this was not possible. Because the
179 primary event rates were lower than predicted during the study, the trial recruitment period was
180 extended beyond the two years originally planned and the follow-up period was also extended.

181 **Outcomes**

182 The primary outcome was the composite of: hospitalisation for non-fatal myocardial
183 infarction/biomarker positive acute coronary syndrome, non-fatal stroke (whether reported to have
184 been hospitalised, non-hospitalised or to have occurred during a hospitalisation) or death due to a
185 cardiovascular event.

186 The secondary outcomes were: hospitalisation for non-fatal myocardial infarction/biomarker
187 positive acute coronary syndrome; non-fatal stroke (whether reported to have been hospitalised,
188 non-hospitalised or to have occurred during a hospitalisation); cardiovascular death; all-cause
189 mortality; hospitalisation for heart failure; hospitalisation for unstable, new or worsening angina;
190 hospitalisation for coronary revascularisation; hospitalisation for cerebral revascularisation;
191 hospitalisation for transient ischaemic attack (TIA); hospitalisation for non-fatal cardiac arrest;
192 hospitalisation for venous and peripheral arterial vascular thrombotic event; hospitalisation for
193 arrhythmia with no evidence of ischaemia.

194 Minor amendments to two components of the primary outcome were made during the trial –
195 hospitalised stroke was amended to include strokes that were non-hospitalised or occurred during a
196 hospitalisation, and myocardial infarction was updated to include myocardial infarction or biomarker
197 positive acute coronary syndrome (which are largely considered to be the same outcome nowadays).

198 An independent clinical events classification committee based at the University of Glasgow, whose
199 members were unaware of the trial group assignments, assessed all the components of the primary
200 composite outcome, secondary cardiovascular outcomes, and death; these events are defined in the
201 clinical event definitions (appendix pp7-25).

202 An exploratory efficacy endpoint was also included: the proportion of patients whose serum urate
203 level was < 0.357 mmol/L (< 6 mg/dL), and < 0.297 mmol/L (< 5 mg/dL) after each year of treatment.

204 Serious adverse events occurring during and up to 28 days after the end of the study were recorded
205 unless participants had withdrawn consent. Gout flares and any treatment-related adverse events
206 were also recorded.

207 For adverse events that were potential study endpoints, more detailed information was collected
208 from medical records and death certificates and an anonymised endpoint package was prepared for
209 adjudication by an independent adjudication committee.

210 **Statistical analysis**

211 It was calculated that 456 first primary events were required to show non-inferiority between the
212 febuxostat and allopurinol treatment arms assuming a non-inferiority limit for the hazard ratio of 1·3
213 with 80% power and a one-sided alpha of 0·025. The non-inferiority margin of 1·3 was selected and
214 approved by the EMA as representing a minimal difference of clinical interest and was based on
215 previous regulatory guidance and precedent. Previous and ongoing cardiovascular safety studies
216 have used similar values which have been accepted by regulators, including cardiovascular safety
217 trials of novel treatments for diabetes, trials comparing celecoxib with other non-steroidal anti-
218 inflammatory drugs and ongoing trials of novel renal treatments¹³⁻¹⁷. With an expected primary
219 event rate of about 10% over three years in the allopurinol group based on events observed in
220 observational databases, it was estimated that 2282 patients would be required in each treatment
221 arm. Assuming a dropout rate of 20% from the on-treatment population, the enrolment of 2853
222 patients in each treatment arm (5706 total) was predicted to provide the required number of
223 primary events with an average follow-up period of 3 years. Baseline characteristics are shown
224 according to treatment groups as means (SD) or median (IQR) for continuous variables and as
225 numbers and percentages for categorical variables.

226

227 All clinical outcomes were analysed on a time to first event basis using Cox proportional hazards
228 models, with the exception of the frequency of flares of gout, for which all recurrent events were
229 counted and analysed using a negative binomial regression model. All analyses were adjusted for the
230 stratification variable and country and the treatment effect for febuxostat relative to allopurinol was
231 estimated, reporting hazard ratios and 95% confidence intervals for the Cox models and incidence
232 rate ratio and 95% confidence interval for the negative binomial model. P-values were calculated
233 from Wald statistics. The primary analysis was an on-treatment (OT) analysis. The OT analyses
234 censored follow-up after permanent discontinuation from original randomised therapy, death from
235 any cause not included in the endpoint being considered, date of withdrawal of all consent to

236 participate further in the study or end of study (31 December, 2019), whichever occurred first. The
237 intention to treat (ITT) analysis censored follow-up after death from any cause not included in the
238 endpoint being considered, date of withdrawal of all consent to participate further in the study, or
239 end of study, whichever occurred first. In the OT analyses, the primary outcome was assessed first in
240 an OT non-inferiority analysis with a non-inferiority limit of 1.3. A supporting ITT analysis was
241 conducted and, if non-inferiority was demonstrated in this analysis as well as the OT analysis, an ITT
242 superiority analysis was carried out. This hierarchical testing process meant that there was no need
243 for adjustment for multiple testing. Prespecified subgroup analyses were carried out for the primary
244 endpoint. P values for the test of interaction between the variable defining the subgroup and
245 randomised treatment allocation were calculated. Similar analyses were done for other time-to-
246 event secondary endpoints.

247 Time to event curves are presented as cumulative incidence functions adjusting for the competing
248 risk of deaths not included in the endpoint being plotted.

249 Between treatment group differences in SUA levels were assessed annually using analysis of
250 covariance, adjusting for baseline levels, the stratification variable, and country.

251 The type I error rate was set at 2.5% (one-sided) for the one-sided non-inferiority analyses and at 5%
252 for two-sided superiority analyses. No formal interim analyses were carried out and hence no P-
253 value penalties are required. No adjustments were made for the multiplicity of statistical
254 comparisons. Hence, analyses other than for the primary endpoint should be considered
255 exploratory.

256 All validly randomised participants were included in the OT and ITT analyses. Safety analysis was
257 done for all patients who took at least one dose of randomised medication. The incidence of serious
258 treatment emergent adverse events is summarised by MedDRA system organ class for each
259 treatment group.

260 Analyses and graphical displays were conducted using SAS for Windows version 9.4 and R version
261 3.6.1. All cardiovascular outcomes were adjudicated by an independent clinical endpoint committee
262 (appendix p34), except coronary revascularisation, cerebral revascularisation and TIA which were
263 reviewed and classified by physicians at the University of Dundee.

264 Trial safety was overseen by an independent data monitoring committee (appendix p34). This trial is
265 registered with the EU Clinical Trials Register (EudraCT 2011-001883-23) and ISRCTN
266 (ISRCTN72443728).

267 **Role of the funding source**

268 The study was an investigator-led trial sponsored by the University of Dundee and funded by
269 Menarini. Menarini received support from Ipsen and Teijin Pharma Limited. The funder of the study
270 had no role in study design, data collection, data analysis, data interpretation, writing of the
271 manuscript or the decision to submit. TM, IM, IF and MR had full access to all the data in the study
272 and TM had final responsibility for the decision to submit for publication. The study Clinical Co-
273 ordination Centre was MEMO Research at the University of Dundee and the study Data and
274 Biostatistical Centre was at the Robertson Centre for Biostatistics at the University of Glasgow. Trial
275 monitoring was carried out or subcontracted by the University of Dundee as study sponsor.

276 **Results**

277 From 20 December, 2011, to 17 October, 2017, 6603 patients consented to enrol in the trial and
278 were assessed for eligibility; 475 patients were excluded before randomisation. Data for 14
279 randomised patients and one non-randomised patient (all recruited at one UK site) were deleted
280 from the study database following instruction by the sponsor because of concerns identified at a
281 monitoring visit regarding the validity of consent and inclusion of these patients and their data.
282 These 15 patients are excluded from all summaries and analyses. A total of 6128 patients were
283 randomly assigned to receive febuxostat (n=3063) or allopurinol (n=3065; figure 1). The final

284 randomisation took place on 26 January, 2018. Patients stopped randomised treatment at the end of
285 the trial, on 31 December, 2019. The study reached the end of its contracted period on 31 Dec 2019
286 and the decision to end the trial then was made at a time when the number of adjudicated primary
287 events that had occurred was still uncertain. The final lower than target number of primary events
288 was due to uncertainty about whether some events had occurred 'on treatment' that was later
289 clarified, and a lower than expected number of potential events for which information was still being
290 gathered being adjudicated as positive events. Final record-linkage data and supporting information
291 on endpoints resulted in the trial completion being the end of August 2020. Median follow-up time
292 in the study was 1467 days [IQR 1029-2052] and median on-treatment follow-up period was 1324
293 days [IQR 870-1919].

294 The two treatment groups were well balanced with respect to baseline characteristics (table 1) and
295 baseline cardiovascular risk factors (appendix p26), with the exception of a small excess of history of
296 diabetes mellitus (n=719 (23.5%) in the allopurinol group compared to n=661 (21.6%) in the
297 febuxostat group). The mean age was 71.0 years (SD 6.4), 5225 (85.3%) were male and 6070 (99.1%)
298 were white. 38.9% were recruited in Scotland, 27.3% in England, 31.7% in Denmark, and 2.1% in
299 Sweden. 2046 patients (33.4%) had a history of cardiovascular disease (defined as myocardial
300 infarction, cerebrovascular accident, transient ischaemic attack, acute coronary syndrome, coronary
301 revascularisation, angina pectoris or heart failure). 1380 patients (22.5%) had a history of diabetes
302 mellitus.

303 A total of 3593 patients (58.6%) were taking statins, 2170 patients (35.4%) were taking antiplatelet
304 agents, (including 1828 patients (29.8%) taking aspirin), and 2468 patients (40.3%) were taking an
305 angiotensin-converting enzyme inhibitor at screening.

306 The median duration of allopurinol therapy at time of screening was 6.0 years [IQR 2.1-14.0]. At the
307 screening visit, most participants were taking 100mg-300mg daily dose of allopurinol (100mg (1951
308 patients (31.8%)); 200mg (1066 patients (17.4%)); 300mg (2749 patients (44.9%)). In the allopurinol

309 lead-in phase, 2201 patients (35.9%) required an increase in allopurinol dose to reach EULAR target
310 SUA during the allopurinol lead-in phase. The daily doses of allopurinol taken by participants
311 immediately prior to randomisation are shown in appendix p27. The mean daily dose of allopurinol
312 taken at the end of the lead-in allopurinol up-titration phase was 278mg in the allopurinol group and
313 274mg in the febuxostat group. At the end of allopurinol up-titration, 97.3% and 96.9% in the
314 allopurinol and febuxostat groups respectively were at target urate. After randomisation, 97.5% of
315 febuxostat daily doses were 80mg and 2.5% were 120mg. For allopurinol daily doses, 10.0% were
316 100mg, 23.3% were 200mg, 50.9% were 300mg, 11.9% were 400 mg and 3.9% were 500-900 mg.
317 The mean daily dose of febuxostat during the trial was 81mg. The mean daily dose of allopurinol
318 during the trial was 279mg.

319

320 In the primary on-treatment analysis, febuxostat therapy was non-inferior to allopurinol therapy for
321 incidence of the primary endpoint (172 patients assigned to febuxostat [1.72 events per 100 patient
322 years]) compared with 241 patients assigned to allopurinol [2.05 events per 100 patient years]);
323 adjusted hazard ratio 0.85 [95% CI 0.70-1.03], $p < 0.001$) (figure 2a). The ITT analysis confirmed non-
324 inferiority of febuxostat ($p < 0.001$) (figure 2b)). Superiority of febuxostat for the primary outcome
325 was not demonstrated ($p = 0.19$). Results obtained in on-treatment and intention to treat analyses for
326 all-cause mortality (figure 3a and b), cardiovascular death (figure 3c and d)), and for the other
327 secondary outcomes are presented in tables 2 and 3. In the on-treatment analysis, the upper limit of
328 the hazard ratio for all-cause mortality was below 1.0. There were 174 deaths (1.44/100 patient
329 years) in the allopurinol group and 108 (1.06/100 patient years) in the febuxostat group, HR (95%CI),
330 0.75 (0.59, 0.95). In the intention to treat analysis, there were 263 deaths (2.05/100 patient years) in
331 the allopurinol group versus 222 (1.73/100 patient years) in the febuxostat group, HR (95%CI) 0.84
332 (0.71, 1.01). In contrast there was a nominally significant increase in hospitalisation for arrhythmia
333 with no evidence of ischaemia, with 49 patients (0.385/100 patient years) with an event in the
334 allopurinol group versus 74 patients (0.583/100 patient years) in the febuxostat group.

335 A total of 28 pre-specified analyses were carried out based on subgroups according to baseline
336 characteristics (appendix pp40-43). Only one subgroup analysis reached statistical significance in the
337 interaction test (on-treatment $p=0.001$; intention to treat $p=0.003$). This was for the subgroups
338 defined by pre-randomisation urate levels < 0.297 mmol/L and ≥ 0.297 mmol/L. There was a
339 nominally significant reduction in risk in the febuxostat arm compared to the allopurinol arm in the $<$
340 0.297 mmol/L urate subgroup and no statistically significant difference between the two groups in
341 the ≥ 0.297 mmol/L subgroup for the primary outcome. The analysis for the primary outcome in the
342 subgroup of patients with a history of MI, stroke or acute coronary syndrome showed no significant
343 difference between treatment groups (allopurinol $n=83$ (11.8%), febuxostat $n=65$ (9.5%); adjusted
344 HR 1.02 (95% CI 0.74-1.42); $p=0.202$ (on treatment analysis). In the intention to treat analysis for this
345 subgroup results were similar (allopurinol $n=102$ (14.5%), febuxostat $n=103$ (15.1%); adjusted HR
346 1.07 (95% CI 0.81-1.41); $p=0.119$). On the request of a reviewer, an analysis of the composite
347 primary endpoint replacing CV death with all-cause death (on-treatment and intention to treat) and
348 an on-treatment analysis of the same endpoint but extending the on-treatment period by 90 days
349 are presented in the supplementary appendix (pp36-37) The results of these additional analyses
350 were consistent with the main results presented. An on-treatment analysis of the composite
351 outcome of all-cause mortality, non-fatal myocardial infarction/biomarker positive acute coronary
352 syndrome or non-fatal stroke, with additional adjustment for age, sex, low density lipoprotein and
353 high density lipoprotein cholesterol levels, high sensitivity troponin I levels, systolic blood pressure,
354 smoking status and histories (yes/no) of each of diabetes, hypertension and cardiovascular disease is
355 also presented in the supplementary appendix (p38).

356 There was a greater reduction in urate levels on febuxostat treatment compared to allopurinol
357 treatment. The changes from baseline were compared statistically between the two groups at years
358 1-7. There were significant differences between the two groups ($p<0.0001$) in each year with mean
359 differences greater than 0.08 mmol/L for years one to six. After randomisation, 1044 patients in the
360 allopurinol arm experienced at least one gout flare compared to 1017 patients in the febuxostat

361 arm. The rates of gout flares were 19.85 gout flares/100 patient years for allopurinol and 17.95 gout
362 flares/100 patient years for febuxostat.

363 A total of 3050 patients in the allopurinol group and 3001 patients in the febuxostat group took at
364 least one dose of randomised study medication and were included in the safety population
365 (n=6051). In the febuxostat group, 973 patients [32.4%] discontinued randomised therapy compared
366 with 503 patients [16.5%] on allopurinol. The excess withdrawals and withdrawals from treatment in
367 the febuxostat arm occurred in the first year of follow-up, with most occurring in the first six months
368 (appendix pp38-39). Colchicine was the most commonly dispensed gout flare prophylaxis and was
369 dispensed to 1603 patients in the allopurinol group and 2223 patients in the febuxostat group
370 (appendix p28).

371 A total of 263 (8.6%) patients died and 1812 (59.4%) experienced at least one serious adverse event
372 in the allopurinol group compared to 222 (7.2%) and 1720 (57.3%) in the febuxostat group (Table 4
373 and appendix p30, p32). Differences were seen in the incidence of endocrine disorders, and
374 neoplasms (benign, malignant and unspecified (including cysts and polyps)) between treatment
375 groups. **The upper limit of normal for creatinine was 106 µmol/L in males and 80 µmol/L in females.**
376 **31% of patients had at least one value above this limit in the allopurinol group and 34% in the**
377 **febuxostat group.** Only 24 patients had serious adverse events that were considered treatment-
378 related, 19 in the febuxostat group and 5 in the allopurinol group. There were 28 treatment-related
379 serious adverse events in total. The most obvious difference between treatment groups for
380 treatment-related serious adverse events was for gastrointestinal disorders (8 for the febuxostat
381 group versus 1 for the allopurinol group). In the allopurinol group, the five treatment-related serious
382 adverse events were angina (two cases), thrombocytopenia, dyspepsia and arthralgia (all recovered).
383 In the febuxostat group, the 23 treatment-related serious adverse events in 19 patients were
384 pancreatitis (five episodes in four patients; one patient recovered, two recovered with sequelae;
385 one patient had pancreatitis that recovered, then had a further episode of pancreatitis with

386 gastrointestinal perforation, circulatory collapse and death), diarrhoea (three cases, all recovered,
387 one additionally associated with acute renal failure which recovered), atrial fibrillation (three cases,
388 two recovered, one not recovered), cholecystitis (two cases, one recovered, one recovered with
389 sequelae). The other treatment-related serious adverse events in the febuxostat group were single
390 cases of haematuria and non-cardiac chest pain (recovered), and worsening renal failure, abnormal
391 liver function tests, rotator cuff syndrome and pneumonia (recovered with sequelae). Because all
392 patients were taking allopurinol at baseline, those randomised to the allopurinol group were
393 inherently less likely to experience treatment-related serious adverse events during the trial, than
394 those allocated to the febuxostat group (a novel treatment). More patients overall were reported to
395 be suffering from a malignant neoplasm in the allopurinol arm 384 (12.6%) versus 322 (10.7%) in the
396 febuxostat arm (appendix p31). In the 28 day period following the end of the study, four deaths
397 were reported in each treatment group.

398 **Discussion**

399 This FAST study has clearly demonstrated that in more than 6000 patients with gout receiving ULT
400 with a xanthine oxidase inhibitor at doses designed to lower the urate to EULAR target levels
401 $<0.357\text{mmol/L}$ for up to seven years, febuxostat was non-inferior to allopurinol with regard to the
402 occurrence of major cardiovascular outcomes comprising the primary outcome of hospitalisation for
403 non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke or
404 death due to a cardiovascular event. This was demonstrated in both the primary on-treatment and
405 intention to treat analyses. Importantly, there was no signal of increased mortality, with a lower rate
406 of all-cause deaths and cardiovascular deaths reported in the febuxostat group than in the
407 allopurinol group. This contrasts with the findings of the North American Cardiovascular Safety of
408 Febuxostat or Allopurinol in Patients with Gout trial (CARES) which reported that in patients with
409 gout and established cardiovascular comorbidities at baseline, while febuxostat was non-inferior to
410 allopurinol with respect to rates of the primary endpoint of the study (a composite of death from
411 cardiovascular causes, myocardial infarction, stroke, or unstable angina with urgent

412 revascularisation), the rates of the secondary outcomes of adverse cardiovascular outcomes, all-
413 cause death and cardiovascular death were significantly higher with febuxostat than with
414 allopurinol.¹⁷ However, when efforts were made to trace patients in CARES lost to follow-up, this
415 mortality difference was no longer seen, and it was unclear why increased mortality was associated
416 with lower doses of febuxostat. This could simply have been information bias caused by the inability
417 to adequately follow up those who withdrew from CARES. The supporting analyses of CARES where
418 private investigators followed up the vital status of those who withdrew found that the signal of
419 increased mortality was no longer significant and supports this view.

420 Although of similar size, there are several differences between the CARES trial and the FAST trial. All
421 patients in CARES had established cardiovascular disease, while only 33% of patients in FAST had
422 cardiovascular disease at baseline. CARES included patients with severe heart failure who might have
423 particularly poor cardiovascular prognosis, whereas FAST excluded patients with NYHA III or IV heart
424 failure. The prevalence of tophi was greater in the CARES population, suggesting more severe gout at
425 baseline. CARES allowed inclusion of newly treated patients, while FAST only recruited patients who
426 were already established on allopurinol therapy and may therefore have had a lower urate crystal
427 burden, which might be important for cardiovascular risk. To what extent the results of FAST are
428 generalisable to patients with gout who have not previously been treated with ULT, or to patients
429 with severe heart failure is not clear. The doses of randomised medication were different in the two
430 trials, with a lower dose of febuxostat being used in CARES (40-80mg daily) compared with FAST
431 (80mg-120mg daily) and the range of doses of allopurinol differed (200-600mg daily in CARES; 100-
432 900mg daily in FAST), reflecting the different dose ranges for the two XOIs approved by regulatory
433 agencies in North America and Europe. In the CARES trial, 56.6% of patients discontinued
434 randomised treatment prematurely and 45.0% of patients withdrew and did not complete all trial
435 visits and were therefore not followed up until the end of the trial. In the FAST study, there were
436 lower rates of treatment discontinuation (16.5% in the allopurinol group and 32.4% in the febuxostat

437 group) and much better rates of patient follow up with only 5.8% of patients in FAST withdrawing
438 from all follow up.

439 The results of the CARES study led to regulators issuing alerts from 2017 onwards and subsequently
440 changing prescribing advice for febuxostat and recommending that treatment with febuxostat
441 should be avoided in patients with pre-existing major cardiovascular diseases (e.g. myocardial
442 infarction, stroke or unstable angina), unless no other therapeutic options are appropriate. At the
443 time this advice was released in Europe and the UK, the Medicines and Healthcare Regulatory
444 Agency (MHRA) requested that the FAST investigators should provide an updated risk-benefit
445 assessment about whether the study should continue. An independent risk-benefit assessment led
446 to the MHRA making the recommendation in 2018 that FAST should continue unchanged. However,
447 it is likely that the regulatory advice released to healthcare professionals at this time may have
448 increased withdrawals from randomised medication in the febuxostat arm of the study. Notably, no
449 increased risk of adverse cardiovascular events was found in the FAST subgroup of patients with
450 prior MI, stroke or acute coronary syndrome, who were very similar to the patients included in the
451 CARES study.

452 The FAST study finished underpowered for the required number of primary events, with 413 events
453 instead of the planned target of 456 events. The lower number of primary events will have resulted
454 in only a modest reduction in statistical power from 80% to approximately 77% to exclude a non-
455 inferiority limit of 1.3, or alternatively, 80% power to exclude a non-inferiority limit of 1.315.

456 The primary analysis of FAST, endorsed by the EMA, was an on-treatment rather than intention-to-
457 treat analysis, as is commonly the case in a non-inferiority safety trial. In such trials, on-treatment
458 analysis results in a comparison that is undiluted by periods when the medications under
459 investigation were not taken. In FAST, our research pharmacy had regular contact with all trial
460 participants about adherence so our ascertainment of exposure to randomised medications was
461 good. However, an on-treatment analysis may not provide a true unbiased analysis of the

462 randomised population if there are differential discontinuation rates, as indeed there were in FAST,
463 with higher discontinuation rates and earlier discontinuations of febuxostat than allopurinol. This
464 could have been influenced by the higher use of colchicine in patients randomised to febuxostat and
465 the fact that switching from any established drug therapy to a new drug therapy usually results in
466 more discontinuations in trials. For this reason, a supporting ITT analysis was also done. Because we
467 were able to follow up patients until the end of the trial by telephone and other personal contact
468 and by record-linkage to national hospitalisation and death records (except for the small proportion
469 who withdrew completely), our ascertainment of outcomes in the ITT analysis was very good. Both
470 analyses provided similar mortality findings.

471 Although an association between serum urate concentrations and cardiovascular disease is well
472 established from numerous observational studies the hypothesis that hyperuricaemia has a direct
473 causal role in the aetiopathogenesis of comorbid cardiovascular disease remains controversial and is
474 not supported by Mendelian randomisation studies.^{18,19}

475

476 Colchicine use was greater in the febuxostat group, probably because more patients switching
477 therapy to febuxostat chose to accept gout flare prophylaxis than those continuing on allopurinol.

478 Although some recent trials have demonstrated that treatment with colchicine improved outcomes
479 in patients with recent myocardial infarction, and chronic coronary disease, published evidence that
480 treatment with colchicine may be associated with improvements in cardiovascular outcomes has
481 been inconsistent.²⁰⁻²³ In FAST, while prophylaxis against flares of gout was offered to all patients,
482 only some accepted it, those who took it mainly did so at the very beginning of the trial, and it is
483 likely that some patients chose to take it for less than the six months provided. **It is unlikely that the**
484 **relatively short-term administration of low dose colchicine or NSAIDs as prophylaxis, or any**
485 **differences in concomitant use of colchicine or NSAIDs, even with the imbalances between**
486 **treatment groups, had any major effect on the long-term outcomes of FAST. A new figure has been**

487 added to the supplementary appendix (Figure S5, pp50-51) to show the effects of prophylaxis or
488 concomitant use of NSAIDs or colchicine.

489 As neither the FAST nor CARES trial had a placebo arm for comparison against active treatment with
490 XOI, it is possible that either or both XOIs may actually protect patients with gout against
491 cardiovascular disease and mortality. Certainly, the cardiovascular event rates in the FAST study
492 were lower than anticipated. A large randomised trial comparing allopurinol 600mg daily therapy
493 versus usual care, the ALL-HEART study,²⁴ is currently underway in the UK to determine if allopurinol
494 has a beneficial effect on major cardiovascular outcomes in patients with ischaemic heart disease
495 (IHD). Should allopurinol be of benefit in IHD, a case could be made to carry out a randomised trial of
496 febuxostat vs usual care or placebo in patients with cardiovascular disease.

497 Other findings of FAST may deserve further research. One possibility is to investigate the findings of
498 numerically higher non-CV deaths and malignancies with allopurinol than febuxostat. Another is to
499 investigate the higher rate of hospitalisations for arrhythmias without evidence of ischaemia found
500 in FAST.

501 In summary, we found that febuxostat 80-120mg was non-inferior to allopurinol 100-900mg with
502 respect to its impact on adverse cardiovascular events. In contrast to a previous large study, we
503 found no signal of increased all-cause or cardiovascular mortality with febuxostat. In the light of
504 these findings, regulatory advice to avoid the use of febuxostat in patients with cardiovascular
505 disease should be reconsidered and modified.

506 **Contributors**

507 The idea for the study was conceived by TM. TM, IF and GN formed the Executive Committee of the
508 trial. TM, IF, GN and IM participated in the design of the study. MR and IF did the statistical analysis.
509 IM wrote the first draft of the manuscript with input from IF and TM. All authors participated in the

510 interpretation of the data, and critical review of the manuscript. All authors have read and approved
511 the final version.

512 **Declaration of interests**

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526 Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Novartis,
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532

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540

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Figure 3:

(a) Cumulative incidence functions for all-cause mortality (on-treatment analysis) (n=6128).

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