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1 **A Placebo-controlled Trial of Bezafibrate in Primary Biliary Cholangitis**

2

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48

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51

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68

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72 **BACKGROUND**

73 Patients with primary biliary cholangitis (PBC) who inadequately respond to ursodeoxycholic  
74 acid (UDCA) therapy are at high risk of disease progression. Fibrates, which are agonists of  
75 peroxisome proliferator-activated receptors, in combination with UDCA, have shown  
76 potential benefit in this condition.

77 **METHODS**

78 In this 24-month, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 100  
79 patients who had an inadequate response to UDCA according to the Paris-2 criteria to  
80 receive bezafibrate, at a daily dose of 400 mg (n=50), or placebo (n=50), in addition to  
81 continued treatment with UDCA. The primary outcome was a complete biochemical  
82 response defined as normal levels at 24 months of all of the following: total bilirubin,  
83 alkaline phosphatase (ALP), aminotransferases, albumin, and prothrombin index.

84 **RESULTS**

85 The primary outcome occurred in 30% of patients with bezafibrate and 1% with placebo  
86 (difference [95%CI] = 29% [16% ; 43%];  $P < 0.001$ ). Normalization of ALP occurred in 67% of  
87 patients with bezafibrate and 2% with placebo. Changes in pruritus, fatigue, and non-  
88 invasive markers of liver fibrosis, including liver stiffness measurement and Enhanced Liver  
89 Fibrosis score, were consistent with the primary outcome. Two patients in each group  
90 experienced end-stage liver complications. Creatinine level increased 5% in the bezafibrate  
91 group and decreased 3% in the placebo group. Myalgia was experienced by 20% in  
92 bezafibrate and 10% in placebo group.

93 **CONCLUSIONS**

94 Bezafibrate administered with UDCA in patients with PBC who had inadequate response to  
95 UDCA alone resulted in a significantly higher rate of complete biochemical response than

96 placebo with UDCA. (Funded by the Assistance Publique–Hôpitaux de Paris with support  
97 from Arrow Génériques; BEZURSO ClinicalTrials.gov number, NCT01654731).

98 Primary biliary cholangitis (PBC) is a progressive liver disease of unknown cause that  
99 mainly affects women over the age of 30. It is characterized by serum autoantibodies,  
100 inflammation and destruction of small intrahepatic bile ducts, progressive cholestasis, a  
101 distinctive symptom of which is pruritus, and slow progression towards cirrhosis and liver  
102 failure.<sup>1</sup> Ursodeoxycholic acid (UDCA), a hydrophilic bile acid with choleric and liver-  
103 protective properties, is currently the standard first-line therapy for PBC.<sup>2,3</sup> Treatment with  
104 UDCA improves biochemical markers of cholestasis and delays the time to liver  
105 transplantation.<sup>4,5</sup> However, long-term survival remains impaired in patients with  
106 incomplete biochemical response.<sup>6-8</sup> Additional therapeutic options are therefore needed in  
107 patients who have an inadequate response to UDCA.

108 Combination of obeticholic acid (OCA), a selective agonist of the farnesoid X receptor,  
109 with UDCA has recently been shown to decrease biochemical markers of cholestasis in  
110 patients with PBC who have inadequately responded to UDCA.<sup>9,10</sup> In these studies, however,  
111 OCA was associated with higher rates of severe pruritus than placebo.<sup>10</sup> Alternatively,  
112 association of UDCA with fibrates, that are agonists of peroxisome proliferator-activated  
113 receptors (PPAR), might have the potential to improve both biochemical parameters and  
114 symptoms of PBC.<sup>11-14</sup> The aim of the present trial was to assess the efficacy, safety, and  
115 adverse-event profile of bezafibrate, a pan-PPAR agonist, in patients with PBC who despite  
116 UDCA treatment continue to exhibit significant alteration in biochemical liver tests.

117

118 **METHODS**

119

120 **Participants**

121 Patients aged 18 or older who had been diagnosed with PBC according to established  
122 criteria<sup>2</sup> were recruited from 21 centers throughout France. All patients were treated with  
123 UDCA at a dose of 13-15 mg/kg/d. Entry criterion was an inadequate biochemical response  
124 to UDCA as defined by the Paris-2 criteria<sup>15</sup>, i.e. a serum level of alkaline phosphatase (ALP)  
125 or aspartate aminotransferase (AST) > 1.5 times the upper limit of the normal range (ULN) or  
126 an abnormal total bilirubin level (< 50 µmole/L), assessed after 6 months of treatment or  
127 more. All patients gave written informed consent. The protocol, available with this article at  
128 [nejm.org](http://nejm.org), was approved by the Committee for the Protection of Persons and the French  
129 National Agency for Medicines and Health Products Safety. The authors vouch for fidelity of  
130 this report to the protocol and for the completeness and accuracy of the data and data  
131 analyses.

132

133 **Trial design**

134 The study was designed as a 2-arm, randomized, double-blind, placebo-controlled trial.  
135 Centralized balanced block randomization (blocks of size 4) was computer generated  
136 without stratification by center. Patients were randomly assigned, in a 1:1 ratio, to receive  
137 once-daily oral placebo or bezafibrate at a dose of 400 mg in combination with UDCA  
138 therapy. They were followed-up every 3 months during 24 months. Ultrasound (US) of the  
139 liver and liver stiffness measurement were performed at baseline, 12, and 24 months. Liver  
140 stiffness measurement was assessed using vibration-controlled transient elastography



141 (Fibroscan, Echosens, France); liver stiffness measurements correlate with histological  
142 fibrosis and prognosis.<sup>16</sup>

143

#### 144 **Primary, secondary, and exploratory outcomes**

145 The primary outcome was the percentage of patients with a complete biochemical response  
146 as defined by normal serum levels at 24 months of all of the following: ALP, AST, alanine  
147 aminotransferase (ALT), total bilirubin, albumin, and prothrombin index.

148 Secondary outcomes included the percentage of patients with the above-defined response  
149 at the different time points of the study, the percentage of patients with normal ALP at 24  
150 months, changes in serum levels of ALP, AST, ALT, gammaglutamyl transpeptidase (GGT),  
151 total bilirubin, albumin, prothrombin index, total, high and low density lipoprotein (HDL,  
152 LDL) cholesterol, and platelets count, the percentage of patients with an adequate  
153 biochemical response at 24 months, changes in itch intensity score (0-10 visual analogue  
154 scale (VAS), 10 indicating worse itch),<sup>17</sup> fatigue (absent, intermittent, continuous) and quality  
155 of life (Nottingham Health Profile classified into 6 domains of well-being, each of which  
156 being scored from 0 (better) to 100 (worse)),<sup>18</sup> changes in liver stiffness measurement.

157 Secondary outcomes also included changes in Enhanced Liver Fibrosis score (a validated  
158 measure of liver fibrosis based on the serum levels of hyaluronic acid, procollagen type III N-  
159 terminal peptide, and tissue inhibitor of metalloproteinase 1),<sup>19</sup> development of portal  
160 hypertension (defined as meeting at least one of the following criteria: ascites, esophageal  
161 or gastric varices, US signs of portal hypertension, platelet count < 150 G/L, or liver stiffness  
162 measurement > 20 kPa), and survival without liver transplantation or liver complications  
163 (defined as ascites, variceal bleeding, hepatic encephalopathy, or a doubling of total bilirubin  
164 level > 50  $\mu$ mole/L).

165 Post-hoc exploratory outcomes included changes in serum levels of total and endogenous  
166 bile acids (BA), UDCA, 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4 bile acid precursor),  
167 immunoglobulins M (IgM) and G (IgG), high-sensitivity C-reactive protein (hsCRP), tumor  
168 necrosis factor alpha (TNF- $\alpha$ ), and interleukin 12 (IL-12), survival estimated according to the  
169 Globe and UK-PBC risk scores (see supplementary appendix), and predictive factors of  
170 inadequate response.

171

## 172 **Safety reports**

173 Adverse events were summarized according to the Medical Dictionary for Regulatory  
174 Activities (MedDRA) System Organ Class version 20.0, the MedDRA preferred term, severity  
175 and causal relationship as assessed by the investigators.

176

## 177 **Statistical analysis**

178 Based on the results of a 2-year, open-label pilot study of 38 patients followed at Saint-  
179 Antoine Hospital, Paris, France, treated with UDCA (13-15 mg/kg/d) and fibrates (bezafibrate  
180 400 mg/d or fenofibrate 200 mg/d) combination therapy (unpublished data, available on  
181 request), we expected a rate of complete biochemical response of 40% in the bezafibrate  
182 group and 10% in the placebo group. We decided to opt for bezafibrate, a pan-PPAR agonist,  
183 because of better-documented effects and broader expected properties. Considering a 2-  
184 sided 5%-alpha risk and a 17% lost-to-follow-up rate, 100 patients were needed to achieve  
185 90% statistical power.

186 Analyses were performed at the end of the trial on the intent-to-treat population (all  
187 randomized patients), and blinded to treatment allocation. Multiple imputation was

188 performed to replace missing biochemical parameters used to assess the primary outcome.  
189 The difference in response rates and its 95% confidence interval (95%CI) were estimated and  
190 treatment groups were compared using chi-square test. Sensitivity analyses (no imputation,  
191 last observation carried forward and worst-case scenario methods) were performed.  
192 Quantitative data were expressed as mean and standard deviation (SD) or median and  
193 interquartile range when appropriate and mean difference between bezafibrate and placebo  
194 groups and 95% CI. Piecewise linear mixed-effects models were used to explore some critical  
195 parameters overtime after log-transformation, considering random effects for time and  
196 subject. Knots were not pre-specified. Logistic regression analysis was used to study the  
197 predictive factors of inadequate biochemical response. All tests were two-sided and a P-  
198 value < 0.05 indicated statistical significance. No adjustment for multiple comparisons was  
199 planned, and 95%CI, without p values, are reported for the secondary outcome and  
200 exploratory analyses. A total of 44 tests were conducted for secondary outcomes. Given the  
201 number of tests conducted, the 95%CI may not be reproducible. Analyses were performed  
202 using SAS version 9.3, SAS institute Inc., Cary, USA. See supplementary appendix for  
203 additional details.

204

## 205 **RESULTS**

206

### 207 **Trial populations**

208 One hundred patients (n=50 in each group) were enrolled between September 2012 and  
209 December 2014 (Fig. S1 in supplement appendix). Baseline characteristics of patients did not  
210 differ between groups (**Table 1**). Overall, 95% were female, mostly of Caucasian origin, with  
211 an average age of 53 ± 10 years. Forty percent of patients had significant (VAS ≥ 3) pruritus

212 and 48% declared intermittent or continuous fatigue. Half (54%) was at an advanced stage of  
213 disease according to histology (Ludwig's stage 3 or 4) or liver stiffness measurement (> 9.6  
214 kPa).

215

### 216 **Study and drug discontinuation**

217 A total of 92 (92%) patients completed the trial. Early termination of the study occurred in 2  
218 (4%) patients in the bezafibrate group and 6 (12%) patients in the placebo group. Temporary  
219 or definitive cessation of the randomized treatment occurred in 13 patients in placebo vs. 7  
220 patients in bezafibrate group; cessation of UDCA occurred in 4 patients in placebo vs. 2  
221 patients in bezafibrate group.

222

### 223 **Primary outcome**

224 The primary outcome was achieved in 30% of patients in the bezafibrate group and 1% in  
225 the placebo group (difference [95%CI] = 29% [16% ; 43%]; P < 0.001). The conclusion  
226 remained unchanged in sensitivity analysis (Table S1 in supplement appendix). The rate of  
227 complete biochemical response in the bezafibrate group increased progressively during the  
228 first 15 months of treatment before reaching a plateau of 30-35% (**Fig. 1**).

229

### 230 **Secondary outcomes**

231

#### 232 *Biochemical parameters*

233 The specific changes in total bilirubin, ALP, GGT, ALT, albumin, platelet count, and total  
234 cholesterol were consistent with the primary outcome (**Table 2**). At 24 months, 31 (67%)  
235 patients in the bezafibrate group and 1 (2%) patient in the placebo group had normal ALP

236 levels (difference [95%CI] = 65% [47% ; 79%]). A 60% median reduction in ALP was observed  
237 in the bezafibrate group from month 3 (**Fig. 2A**). A similar rapid reduction in GGT was  
238 observed among bezafibrate users (Fig. S2 in supplement appendix). These results were  
239 confirmed in longitudinal analysis (Tables S2 and Table S3 in supplement appendix). Total  
240 bilirubin showed a 14% decrease in the bezafibrate group and a 18% increase in the placebo  
241 group (**Fig. 2B** and Table S4 in supplement appendix). The course of bilirubin in cirrhotic  
242 patients did not differ between groups. Aminotransferases in the bezafibrate group  
243 decreased progressively (**Fig. 2C** and Fig. S3 in supplement appendix; Tables S5 and Table S6  
244 in supplement appendix). Three months after the end of study (washout period of allocated  
245 treatment), total bilirubin, ALP, GGT, and aminotransferases deteriorated in the bezafibrate  
246 but not the placebo group (Fig. S4 in supplement appendix).

247

#### 248 *Predefined biochemical responses*

249 The rates of adequate biochemical response as defined by established criteria (Barcelona,  
250 Paris-1, Paris-2, Rotterdam, Toronto, and Globe score) were significantly higher in the  
251 bezafibrate than in the placebo group, except for the Rotterdam criteria that were expected  
252 to deteriorate only in late-stage disease (Table S7 in supplement appendix).

253

#### 254 *Patient-reported outcomes*

255 Changes in itch intensity score were consistent with the primary outcome (Fig. S5 in  
256 supplement appendix), as were changes in fatigue status (Table S8 in supplement appendix).  
257 No differences were found in the quality-of-life scores (Table S9 in supplement appendix).

258

#### 259 *Noninvasive markers of fibrosis*

260 Changes in liver stiffness measurement at 24 months showed a 15% decrease in the  
261 bezafibrate group and a 22% increase in the placebo group (difference [95%CI] = -48% [-82%  
262 ; -13%]; **Fig. 2D**). Changes in Enhanced Liver Fibrosis score were consistent with this result  
263 (difference [95%CI] = -4% [-8% ; -1%]; Table S10 in supplement appendix).

264

#### 265 *Liver histology*

266 Histological data were available in 59 patients at baseline (bezafibrate: 30, placebo: 29) and  
267 51 patients at 24 months (bezafibrate: 26, placebo: 25), but only 28 patients had available  
268 data at both time points. Among this subgroup, changes in histological stage, fibrosis stage,  
269 and activity grade did not differ between treatment arms.

270

#### 271 *Clinical outcomes*

272 Nineteen patients developed features of portal hypertension with no difference between  
273 groups (20% in the bezafibrate vs. 18% in the placebo groups). Four patients, 2 in each  
274 group, experienced liver complications: one liver transplantation and one inscription on  
275 waiting list in the bezafibrate group, one ascites and one doubling of total bilirubin > 50  
276  $\mu\text{mole/L}$  in the placebo group. No patients died.

277

#### 278 **Post hoc analyses**

279

#### 280 *Serum bile acids and C4 precursor*

281 At baseline, serum levels of total and endogenous BA, UDCA, and C4 precursor (a marker of  
282 BA synthesis) did not differ between groups (Table S11 in supplement appendix). Changes in  
283 C4 precursor were consistent with the primary outcome (Fig. S6 in supplement appendix).

284 Changes in total and endogenous BA levels did not differ between groups, but the  
285 proportion of endogenous BA within the BA pool significantly decreased with bezafibrate  
286 (Table S12 in supplement appendix).

287

#### 288 *Markers of immunity and inflammation*

289 In the subgroup of patients with available data, changes in serum IgM and IgG levels did not  
290 differ significantly between groups (Fig. S7A in supplement appendix). No difference was  
291 found in hs-CRP, TNF- $\alpha$ , and IL-12 serum level changes (Fig. S7B in supplement appendix).

292

#### 293 *Predictive factors of inadequate response*

294 The factors that were independently associated with an inadequate biochemical response to  
295 bezafibrate were features of portal hypertension and ALP level (Table S13 in supplement  
296 appendix).

297

#### 298 *Prognostic scores*

299 The application of the Globe and UK-PBC risk scores at baseline, 12 and 24 months showed a  
300 significant reduction in the predicted rates of liver transplantation and death in the  
301 bezafibrate vs. placebo group (Fig. S8 in supplement appendix).

302

#### 303 **Safety and side-effects**

304

305 Overall, 424 adverse events were reported in 88 patients and were distributed as follows:  
306 49% in bezafibrate, 51% in placebo group (**Table 3**).

307 A total of 39 (9%) serious adverse events (SAE) was reported in 26 patients, 14 patients in  
308 bezafibrate and 12 patients in placebo group (Table S14 in supplement appendix).  
309 Creatinine levels increased 5% in the bezafibrate group and decreased 3% in the placebo  
310 group (difference [95%CI] = 11% [5% ; 18%]). This difference was noticeable at month 3 and  
311 remained stable during the study (Fig. S9 in supplement appendix). One patient in the  
312 bezafibrate group (with history of diabetes and hypertension) showed a decrease in  
313 estimated glomerular filtration rate (eGFR) to < 60 mL/min (stage 3 renal disease). Ten  
314 patients (4 in bezafibrate, 6 in placebo group) met stage 2 renal disease (eGFR  $\geq$  60 and < 90  
315 mL/min) at 24 months.  
316 Four patients experienced an increase in aminotransferases > 5 times the ULN, one in  
317 placebo and 3 in bezafibrate group. This led to a definitive cessation of allocated treatment  
318 in 3 patients (one in placebo, 2 in bezafibrate group). All cases in the bezafibrate group  
319 resolved within 3 months, either spontaneously (one patient) or after corticosteroids  
320 administration (2 patients in whom liver histology at baseline was suggestive of associated  
321 autoimmune hepatitis).  
322 Myalgia was experienced by 20% in bezafibrate and 10% in placebo group. One patient in  
323 the bezafibrate group, who concomitantly received statin therapy, developed moderate,  
324 asymptomatic rhabdomyolysis at month 3 that resolved after treatment discontinuation.

325

## 326 **DISCUSSION**

327

328 In this randomized trial, we found that in patients with PBC who had inadequately  
329 responded to UDCA, approximately a third of the patients in the bezafibrate group, as  
330 compared to none in the placebo group, reached the primary outcome, i.e. normal levels of



331 the main biochemical markers of the disease at 24 months. Parallel changes in pruritus,  
332 fatigue, and noninvasive markers of liver fibrosis were consistent with this result.

333 Patients were selected based on the Paris-2 criteria<sup>15</sup>, which have been recognized as  
334 relevant predictors of clinical outcomes in several independent populations of PBC  
335 patients.<sup>20,21</sup>

336 In the present trial, bezafibrate was associated with a rapid and sustained fall in ALP  
337 level and a parallel decrease in total bilirubin, the 2 most important prognostic indicators in  
338 PBC.<sup>21</sup> Despite initial concerns,<sup>22</sup> we did not observe an increase in bilirubin level in cirrhotic  
339 patients who were treated with bezafibrate.

340 These changes were accompanied by a decrease in liver stiffness measurement and  
341 Enhanced Liver Fibrosis score, two markers of liver fibrosis and prognosis of PBC.<sup>16,19</sup> Our  
342 histological data, unfortunately, were too limited to determine if these changes were related  
343 to an effective reduction in liver fibrosis and hepatic inflammation.

344 The trial was not large or long enough to assess the effect of bezafibrate on hard  
345 outcomes. Larger trials will be required to assess effects on liver transplantation and  
346 mortality.

347 Portal hypertension and high ALP level were identified at baseline as independent  
348 predictors of treatment failure. Advanced cirrhosis and severe cholestasis should therefore  
349 be considered as potential limiting factors for adjunctive therapy with bezafibrate.

350 Bezafibrate was associated with a 5% increase in serum creatinine level. This is a  
351 known effect of PPAR- $\alpha$  agonists.<sup>23-25</sup> Its mechanism may involve renal haemodynamic  
352 changes or an increased creatinine release by muscle.<sup>26</sup> One patient in this trial, who had  
353 diabetes and hypertension, developed stage 3 renal disease during treatment with

354 bezafibrate. As a precaution, bezafibrate use should be evaluated with regard to the kidney  
355 function, especially in patients with diabetes, hypertension, or any known renal disease.

356 Different mechanisms may lead to the therapeutic effects described above.<sup>27,28</sup> Our  
357 results support that bezafibrate acts in part through specific anticholestatic properties such  
358 as inhibition of BA synthesis and consequent reduction in endogenous BA overload.<sup>29</sup>  
359 Previous findings have suggested a suppressive effect of fibrates on immune response.<sup>13,30</sup>  
360 We found no significant changes in IgM, hs-CRP, TNF- $\alpha$  and IL-12 serum levels but  
361 suppression of intrahepatic pro-inflammatory cytokines is highly plausible.<sup>31</sup> Finally, the  
362 PPAR- $\delta$  agonistic effects of bezafibrate may be considered specifically as seladelpar, a  
363 selective PPAR- $\delta$  agonist, has recently been shown to improve markers of cholestasis in  
364 patients with PBC.<sup>32</sup>

365 In conclusion, in patients with PBC and inadequate response to UDCA, 24-month add-  
366 on therapy with bezafibrate achieved a higher rate of complete biochemical response than  
367 placebo. Parallel changes in patient-reported outcomes and non-invasive markers of liver  
368 fibrosis were consistent with this effect. Bezafibrate was associated with an increase in  
369 creatinine level. Longer and larger studies are required to assess the effects of bezafibrate  
370 on clinical outcomes.

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- 452

453

454 **Table 1. Demographic and clinical characteristics of the patients at baseline.**

<b>Characteristic</b>	<b>Placebo group (n=50)</b>	<b>Bezafibrate group (n=50)</b>
Age – yr.	53 ± 11	53 ± 9
Age at diagnosis – yr.	49 ± 11	46 ± 7
Female sex – no. (%)	46 (92)	49 (98)
Caucasian origin – no. (%)	48 (96)	47 (94)
UDCA daily dose – mg/kg	15 (14 – 16)	15 (13 – 16)
Fatigue – no. (%)	29 (58)	29 (58)
Significant pruritus – no. (%)	24 (48)	16 (32)
Total bilirubin – μmole/L	12.6 ± 6.8	14.0 ± 7.6
ALP – U/liter	242 (186 – 344)	244 (211 – 308)
AST – U/liter	45 (33 – 64)	44 (33 – 57)
ALT – U/liter	53 (34 – 72)	55 (37 – 73)
GGT – U/liter	164 (100 – 273)	162 (112 – 240)
Albumin – g/L	41.9 ± 2.7	41.3 ± 3.6
Prothrombin index – %	104 ± 15	105 ± 12
Platelet count – G/L	266 ± 74	252 ± 71
Total cholesterol – mmole/L	6.7 ± 1.3	6.4 ± 1.4
Liver stiffness measurement – kPa	11.4 ± 7.9	12.8 ± 12.6
Advanced disease – no. (%)	26 (52)	28 (56)
<b>Disease stage:</b>		
Stage 1 – no. (%)	18 (37)	13 (28)
Stage 2 – no. (%)	14 (29)	14 (30)
Stage 3 – no. (%)	6 (12)	11 (23)
Stage 4 – no. (%)	11 (22)	9 (19)

455  
 456 Data are preceded by the number (percentage) of missing values. Quantitative data are  
 457 expressed as mean ± SD or median (25<sup>th</sup> percentile – 75<sup>th</sup> percentile) when appropriate.  
 458 Categorical data are expressed as number (%). Fatigue was defined by continuous or

459 intermittent fatigue as reported by patients. Significant pruritus was defined by itch intensity  
460 VAS of 3.0 or more. Liver stiffness measurement was determined by vibration-controlled  
461 transient elastography (Fibroscan, Echosens, Paris, France). On the basis of research by  
462 Corpechot et al.,<sup>16</sup> liver stiffness in patients with PBC was assessed as follows: fibrosis stage F0  
463 was associated with a stiffness of 7.0 kPa or less, stage F1 with a stiffness of 7.1 to 8.6 kPa,  
464 stage F2 with a stiffness of 8.7 to 10.8 kPa, stage F3 with a stiffness of 10.9 to 16.0 kPa, and  
465 stage F4 with a stiffness of 16.1 kPa or more. Advanced disease was defined by liver stiffness  
466 measurement > 9.6 kPa or Ludwig's histological stage 3 or 4. Disease stage was defined by  
467 Ludwig's histological stage when available or by Fibroscan using the thresholds reported above.  
468 Values were missing for the following variables: age at diagnosis (1 patient placebo, 1  
469 bezafibrate); fatigue (1, 0); ALP (1, 0); albumin (3, 2); prothrombin index (0, 2); platelet count  
470 (0, 2); total cholesterol (2, 2); liver stiffness measurement (5, 6); disease stage (1, 3). There  
471 were no significant (a p-value < 0.05 level) differences between groups for any of the above  
472 baseline characteristics.

473 **Table 2. Relative changes from baseline to 24 months in biochemical parameters.**

Parameter	Placebo group		Bezafibrate group		Mean difference [95%CI]
	Missing n (%)	% change	Missing n (%)	% change	
Total bilirubin	7 (14)	18 (0 ; 40)	4 (8)	-14 (-33 ; 6)	-26 [-46 ; -6]
ALP	8 (16)	0 (-14 ; 20)	4 (8)	-60 (-66 ; -46)	-59 [-70 ; -49]
GGT	7 (14)	7 (-14 ; 51)	4 (8)	-38 (-59 ; -24)	-71 [-114 ; -28]
AST	7 (14)	8 (-17 ; 26)	4 (8)	-8 (-30 ; 3)	-17 [-34 ; 1]
ALT	7 (14)	0 (-24 ; 31)	4 (8)	-36 (-53 ; -14)	-35 [-55 ; -16]
Albumin	12 (24)	-3 (-7 ; 3)	7 (14)	0 (-4 ; 7)	4 [0 ; 8]
Platelet count	8 (16)	-2 (-16 ; 4)	4 (8)	2 (-8 ; 11)	8 [1 ; 15]
PT index	7 (14)	0 (-8 ; 2)	6 (12)	-2 (-5 ; 0)	1 [-3 ; 4]
Total-C	11 (22)	0 (-9 ; 7)	8 (16)	-16 (-24 ; -9)	-16 [-22 ; -11]
LDL-C	13 (26)	2 (-13 ; 12)	19 (38)	-23 (-31 ; -14)	-26 [-34 ; -18]
HDL-C	13 (26)	-4 (-10 ; 5)	16 (32)	-2 (-13 ; 10)	-4 [-14 ; 5]

474  
475 Relative changes are expressed as median percentage (25<sup>th</sup> percentile – 75<sup>th</sup> percentile). The mean  
476 differences between the bezafibrate and placebo groups are shown with corresponding 95%  
477 confidence intervals (CI). PT denotes Prothrombin. PT index expresses the % of normal plasma  
478 yielding the same PT time. Total-C denotes Total Cholesterol. LDL-C denotes Low-Density Lipoprotein-  
479 Cholesterol. HDL-C denotes High-Density Lipoprotein-Cholesterol. Bezafibrate and placebo were  
480 administered with standard-of-care UDCA.

481

482 **Table 3. Incidence of adverse events of 10% or more and of all serious adverse events.**

<b>Event</b>	<b>Placebo group</b>	<b>Bezafibrate group</b>
Any adverse events	45 (90)	43 (86)
Arthralgia	11 (22)	7 (14)
Myalgia	5 (10)	10 (20)
Nasopharyngitis	10 (20)	9 (18)
Bronchitis	9 (18)	4 (8)
Depressive mood	8 (16)	7 (14)
Abdominal pain	6 (12)	7 (14)
Pruritus	7 (14)	4 (8)
Diarrhea	6 (12)	1 (2)
Flu-like syndrome	5 (10)	5 (10)
Serious adverse events	12 (24)	14 (28)
Transaminase flare > 5 x ULN	1 (2)	3 (6)
Creatinine kinase flare > 5 x ULN	0 (0)	1 (2)
Creatinine increase with worsening of CKD	0 (0)	1 (2)

483  
 484 Shown are the numbers (percentage) of patients with at least one reported event. ULN  
 485 denotes the upper limit of normal range. CKD denotes chronic kidney disease stage. All  
 486 serious adverse events are listed in supplement appendix. Bezafibrate and placebo were  
 487 administered with standard-of-care UDCA.



488 **FIGURE LEGENDS**

489

490 **Figure 1. Percentage of patients with a complete biochemical response according to time**  
491 **and trial group.**

492 The percentage of patients with a complete biochemical response, as defined by normal  
493 serum levels of total bilirubin, ALP, AST, ALT, albumin and prothrombin index, was estimated  
494 from available data at each time point of the trial period in both the placebo (blue columns)  
495 and bezafibrate (orange columns) groups. The number of patients with available data is  
496 shown at each time point for each group. Bezafibrate and placebo were administered with  
497 standard-of-care UDCA.

498

499 **Figure 2. Alkaline phosphatase, total bilirubin, alanine aminotransferase, and liver stiffness**  
500 **measurement according to time and trial group.**

501 The median values of phosphatase alkaline (**Panel A**), total bilirubin (**Panel B**), alanine  
502 aminotransferase (**Panel C**), and liver stiffness measurement (**Panel D**) are shown at each  
503 time point of the trial period in both the placebo (blue circles) and bezafibrate (orange  
504 squares) groups. Lower and upper error bars indicate the 25<sup>th</sup> and 75<sup>th</sup> percentiles,  
505 respectively. ULN denotes the upper limit of the normal range. The number of patients with  
506 available data is shown at each time point for each group. Bezafibrate and placebo were  
507 administered with standard-of-care UDCA.