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The Rationale and Design of Lowering-hyperUricemia Treatment on Cardiovascular Outcomes In Peritoneal DiAlysis Patients: A Prospective, Multicenter, Double-Blind, Randomized Controlled Trial (LUMINA)

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4 1 **The Rationale and Design of Lowering-hyperUricemia Treatment on**
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6 2 **Cardiovascular Outcomes In Peritoneal Dialysis Patients: A Prospective,**
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9 3 **Multicenter, Double-Blind, Randomized Controlled Trial (LUMINA)**
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30 **Keywords:** Hyperuricemia, cardiovascular outcomes, peritoneal dialysis

31

For peer review only

1
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4 325
6 **Abstract**7
8
9 **Objective**10
11 35 To investigate whether lowering hyperuricemia treatment by febuxostat can lower the risk of
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14 36 cardiovascular events in continuous ambulatory peritoneal dialysis (CAPD) patients.15
16
17 **Study Design and Setting**18
19 38 This prospective, multicenter, double-blind, randomized controlled trial was designed to
20
21
22 39 evaluate the effects of lowering hyperuricemia treatment on cardiovascular event risk in
23
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25 40 CAPD patients. Based on a power of 80%, with type I error $\alpha=0.05$, two-sided test, and 1:1
26
27
28 41 parallel control study, a total of 548 eligible patients are expected to be randomly assigned to
29
30
31 42 either lowering hyperuricemia treatment group (febuxostat) or control group (placebo).32
33 **Results**34
35 44 The primary endpoint is cardiovascular events composing of cardiovascular mortality and
36
37
38 45 non-fatal cardiovascular events. All patients will be treated and followed for 3 years.39
40 **Conclusion**41
42
43 47 LUMINA will provide evidence of the effect of lowering-hyperuricemia treatment on
44
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46 48 cardiovascular outcomes in CAPD patients.47
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4950
51 **Strengths and limitations of this study**52
53 51 1. To our knowledge, this is the first large sample size randomized clinical trial to evaluate
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55
56 52 whether high uric acid level is a potentially modifiable risk factor for cardiovascular mortality
57
58
59 53 in peritoneal dialysis patients.

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4 54 2. It is a prospective, multicenter, double-blind, randomized controlled trial powerful enough
5
6
7 55 to test the hypothesis.

8
9 56 3. The LUMINA study has some limitations. Firstly, we recruit prevent and incident patients
10
11
12 57 concurrently, which might have some bias in baseline characteristics

13
14 58 4. Secondly, since center management capability is not parallel in different centers, thus may
15
16
17 59 lead to center bias in the study.

18
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21
22 61 **Trial Registration:** ClinicalTrials.gov

23
24 62 **Trial number:** NCT03200210

25
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27 63 **Registered:** 25 June, 2017

28
29
30 64 The trial was started on July 13, 2017, and was expected to end by December 31, 2012. Till
31
32
33 65 Jan 20, 2020, a total of 548 patients have been recruited.

34
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37
38 67 **Protocol version**

39
40
41 68 The protocol version number and date are YLT-1604-V2.0, December 15, 2016,

42
43 69 **Funding**

44
45
46 70 The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China.

47
48
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50
51
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54 73 Laboratory (2017B030314019), Key Laboratory of Nephrology, Guangdong Province,

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12
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25 83 Drs. Wei Chen and Naya Huang contributed equally to this work.

26
27 84 All authors have made substantial contributions to the work. Contributions of the authors
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30 85 were listed below.

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32 86 Conceptualization: Xueqing Yu

33
34
35 87 Data curation : Wei Chen,

36
37 88 Formal analysis: Qian Zhou, Naya Huang

38
39
40 89 Funding acquisition: Xueqing Yu

41
42 90 Investigation: Naya Huang, Wei Chen, Haiping Mao, Xiao Yang, Qiong Feng

43
44
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48
49
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53
54
55 95 Supervision: Xueqing Yu

56
57 96 Validation: Wei Chen, Xueqing Yu

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4 97 Visualization: Wei Chen, Naya Huang

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46
47
48 136 ***Role of sponsor***

49
50 137 The sponsor participated in the design of the study, but had no role in collection,
51
52 138 management, analysis and interpretation of data, writing of the report, and the decision to
53
54 139 submit the report for publication.

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58 140 ***Composition, roles, and responsibilities of the coordinating centre, steering committee,***

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4 141 *endpoint adjudication committee, data management team, and other individuals or groups*

5
6 142 *overseeing the trial, if applicable (see Item 21a for data monitoring committee)*

7
8
9 143 No applicable.

10
11 144 **Introduction**

12
13 145 *Background and study rationale*

14
15
16 146 Elevated serum uric acid (SUA) seen in patients with chronic kidney disease (CKD) is partly
17
18 147 due to overproduction of purines due to hypercatabolism, and reduced excretion of uric acid
19
20 148 by the kidneys. It was shown that there was a pattern of higher uric acid levels with lower
21
22 149 glomerular filtration rate (GFR) [1-3]. Hyperuricemia is highly prevalent in the general
23
24 150 population with a prevalence of 13.3-42.1% [4-6]. Based on the epidemiological study in
25
26 151 Southern China, prevalence of hyperuricemia in adult population is as high as 31.9% [6].
27
28 152 Reduced GFR seen in CKD patients understandably gives a higher prevalence of
29
30 153 hyperuricemia than that of the general population. Our local data showed that the prevalence
31
32 154 of hyperuricemia in our peritoneal dialysis (PD) center is 63.1% [6].

33
34 155 A lot of epidemiologic and clinical studies have demonstrated a correlation between
35
36 156 hyperuricemia and cardiovascular diseases [7-15]. At the same time, literatures also suggest
37
38 157 hyperuricemia is associated with other classical cardiovascular risk factors such as
39
40 158 hypertension [16], diabetes mellitus [17], hyperlipidemia[18], obesity and insulin resistance
41
42 159 [19, 20]. Evidence shows an elevation in serum uric acid level facilitates oxidation of low
43
44 160 density lipoprotein cholesterol [18], also, hyperuricemia is accompanied with an increase in
45
46 161 free oxygen radical production that plays a role in inflammation [21]. Besides, elevated uric
47
48 162 acid level facilitates the aggregation of platelet, thus increased chance of arterial thrombus

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4 163 formation [22]. These will contribute to higher risk of cardiovascular events.
5
6 164 Treatment of hyperuricemia has been reported to reduce renal disease progression
7
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9 165 independently in CKD patients [23, 24]. And treatment of of hyperuricemia was associated
10
11 166 with lower mortality among hemodialysis (HD) patients with no history of cardiovascular
12
13
14 167 disease (CVD) in Dialysis Outcomes and Practice Patterns Study (DOPPS) study in Japan
15
16
17 168 [25]. Also, in CKD patients, treatment of hyperuricemia has been shown to reduce
18
19 169 cardiovascular risk [26]. However, whether lowering treatment of uric acid would benefit the
20
21
22 170 cardiovascular outcomes in CKD patients, especially in maintenance dialysis patients is not
23
24
25 171 known yet.

172 ***Objectives***

173 To investigate whether lowering hyperuricemia therapy by febuxostat could lower the risk of
174 cardiovascular events in CAPD patients.

175 ***Trial design***

176 The study is a prospective, multicenter, double-blind, randomized controlled trial.

177 **Methods**

178 ***Study setting***

179 The study is conducting in mainland China in 24 academic hospitals. List of study sites can be
180 obtained in the acknowledgements.

181 ***Inclusion criteria:***

182 1. Subjects who are able to understand and have voluntarily signed the informed consent form
183 (ICF)

- 1
2
3
4 184 2. 18-70 years old at the time of randomization
5
6 185 3. Subjects on PD for more than 3 months
7
8
9 186 4. Subjects have hyperuricemia, female: 6mg/dl(360 μ mol/L) <sUA<12mg/dl(720 μ mol/L);
10
11 187 male: 7mg/dl(420 μ mol/L)<sUA<12mg/dl(720 μ mol/L)
12
13
14 188 **Exclusion criteria:**
15
16
17 189 1. Subjects has history of gout
18
19 190 2. Subjects who have a myocardial infarction, unstable angina, cardiovascular reconstructive
20
21 191 surgery (such as a stent or bypass surgery), cerebrovascular accident 12 weeks prior to
22
23 192 randomization, or plan cardiovascular reconstructive surgery during the trial
24
25
26 193 3. Subjects who have New York stage IV heart failure occurs 4 weeks prior to the screening
27
28 194 4. Subjects who have previously received kidney transplantation and are currently prescribed
29
30 195 immunosuppressive therapy
31
32 196 5. Subjects who have severe liver disease, such as acute hepatitis, chronic active hepatitis,
33
34 197 cirrhosis
35
36 198 6. Subjects who have alanine aminotransferase (ALT) greater than 2 folds of the upper limited
37
38 199 of normal or total bilirubin greater than 1.5 folds of upper limited of normal
39
40 200 7. Subjects who have severe infections 4 weeks prior to the screening, such as pneumonia and
41
42 201 peritoneal dialysis-related peritonitis;
43
44 202 8. Subjects who have a major surgery 12 weeks prior to screening or not yet fully recovered
45
46 203 from the surgery
47
48 204 9. Subjects who have a malignancy
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4 205 10. Subjects who report a history of illicit drug use or a regular or daily alcohol consumption
5
6 206 of ≥ 4 alcoholic drinks per day in the 2 years before Screening
7
8
9 207 11. Subjects who are allergic to Febuxostat
10
11
12 208 12. Subjects who are enrolled in other clinical studies within 4 weeks or currently at
13
14 209 randomization
15
16
17 210 13. Subjects who are currently taking mercaptopurine, azathioprine, vidarabine or didanosine
18
19
20 211 14. Subjects who are taking losartan, fenofibrate, thiazide diuretics or loop diuretics within 4
21
22 212 weeks at randomization
23
24
25 213 15. Subjects who require long-term use of steroids (prednisone < 30 mg/d, or equivalent
26
27 214 amount of other steroids and the use of < 2 weeks can be enrolled)
28
29
30 215 16. Subjects who require long-term use of salicylic acid drugs except low-dose aspirin
31
32
33 216 17. Fertility, lactation patients unwilling or unable to use contraception
34

35 217 ***Patient and Public Involvement***

36
37
38 218 We state that patients or the public WERE NOT involved in the design, or conduct, or
39
40 219 reporting, or dissemination plans of our research.
41
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43
44 220 ***Interventions***

45
46 221 Eligible patients will be randomly assigned to febuxostat treatment group or placebo control
47
48 222 group
49

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51 223 ***Dose adjustment***

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53
54 224 Participant is treated by febuxostat/placebo starting at a dose of 20mg /day, once a day. If
55
56 225 SUA doesn't reach the target (SUA < 6 mg/dl), or decrease less than 20% at the 4 weeks' visit,
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4 226 increase dosage to 40mg/d once per day. If SUA doesn't reach target at 8 weeks' visit,
5
6
7 227 increase dosage to (for those who are at dosage of 20mg/day) or maintain dosage (for those
8
9 228 who are at dosage of 40mg/day) at 40mg/d till the end of the study. If at dosage of 40mg/d,
10
11 229 SUA >12mg/dl and last for 2 weeks, patients should withdraw from the study for their safety.
12
13
14 230 If at dose of 40mg/d, SUA <3mg/dl, decrease dose to 20mg/d, and check SUA 2 weeks later,
15
16
17 231 if still <3mg/dl, then stop treatment for 2 weeks and check SUA again, if SUA still <3mg/dl,
18
19 232 withdraw from the study; if SUA \geq 3mg/dl, keep at 20mg/d, till SUA is above target
20
21
22 233 (\geq 6mg/dl), than increase to 40mg/d.
23
24
25 234 If SUA reach target or decrease \geq 20% at the 4 weeks' visit, maintain at the dose of 20mg/d. If
26
27 235 at the dose of 20mg/d, SUA <3mg/dl, then stop treatment and check SUA in 2 weeks, if SUA
28
29 236 still <3mg/dl, withdraw from the study. If SUA \geq 3mg/dl, keep patients in the study, till the
30
31
32 237 SUA is above the target (\geq 6mg/dl) and prescribe from 20mg/d again.
33
34

35 238 ***Criteria for discontinuing or modifying allocated interventions***

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37
38 239 1. Subjects with continued withdrawal of more than 2 weeks or intermittently stopping more
39
40 240 than one month
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43 241 2. Subjects who have intolerable side effects
44
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46 242 3. Subject who have episodes of gout, if SUA<6mg/dl, remain in the trial after acute
47
48 243 treatment; if SUA \geq 6mg/dl, unblind, treat hyperuricemia and withdraw from the trial
49
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51 244 4. Subjects who have no evaluable records available
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54 245 5. Subjects who have to use prohibited medications due to illness
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4 246 6. Subjects who have ALT, AST increased to more than 2 times of upper limit of normal or
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6 247 elevated bilirubin to more than 2 times of the upper limit of normal that has persistently
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9 248 elevated for 2 weeks
- 10
11
12 249 7. Subjects who have SUA > 12 mg/dl for 2 weeks under the maximum dose of treatment (for
13
14 250 how long?)
- 15
16
17 251 8. Subjects who have SUA < 12 mg/dl for 4 weeks under the minimal dose of treatment
- 18
19 252 9. Subjects who have adverse events and cannot continue the study
- 20
21
22 253 10. Subjects who have unexplained complications
- 23
24
25 254 11. Subjects who are pregnant during treatment
- 26
27 255 12. Subjects who have kidney transplantations during the study
- 28
29 256 13. For safety reasons, the organizers propose to stop the study
- 30
31
32 257 14. Ethics Committee decided to discontinue the study subjects
- 33
34
35 258 15. The researchers considered unsuitable for continued research subjects

36
37
38 259 The Investigator may terminate a subject's study participation at any time during the study
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40 260 based on the subject's best interest. In addition, a subject may discontinue his or her
41
42 261 participation at any time during the study.

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45 262 ***Strategies to improve adherence to interventions***

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48 263 Participants will be followed up monthly at the first 3 months at entry of the study and 3
49
50 264 months thereafter till the end of study. Examinations will involve outpatient appointments in
51
52 265 either outpatient clinics or private nephrology practices and will include: History and physical
53
54
55 266 examination, measurement of systolic and diastolic arterial blood pressure, recording of the

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4 267 frequency, type, severity and duration of adverse events as well as laboratory tests including
5
6 268 repeated blood counts.
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9 269 ***Relevant concomitant care permitted or prohibited during the trial***

10
11 270 Medications to treat concomitant conditions are allowed and are recorded at baseline and each
12
13
14 271 follow-up visit. Participants are encouraged to remain on the same dosage of these
15
16
17 272 medications unless advised otherwise by medical professionals. Participants who used
18
19
20 273 diuretics, losartan should be washed out for 2 weeks before screening, patients who used
21
22 274 prednisone ≥ 30 mg/d more than 2 weeks and other drugs treat hyperuricemia other than the
23
24
25 275 assigned trial medications are considered to have dropped out of the trial.
26

27 276 ***Relevant concomitant care permitted or prohibited during the trial included:***

28
29
30 277 1. If taking ACEI/ARB before the trial, can continue but not to increase the dose during the
31
32 278 trial; but need to avoid the use of losartan; if not taking ACEI/ARB, do not add during the
33
34
35 279 study.
36

37 280 2. If SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, adjust the dose of other anti-hypertension drugs
38
39
40 281 except ACEI/ARB

41
42
43 282 3. Lipid-lowering drugs can be used during the study, use statin to treat high cholesterol and
44
45 283 fibrates to treat hypertriglyceridemia mainly in order to maintain normal cholesterol,
46
47
48 284 triglycerides, low-density lipoprotein

49
50
51 285 4. Anti-glycemic drugs can be used, such as insulin, target glycemic control with HbA1c
52
53 286 $< 7.0\%$

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55
56 287 5. Subjects can use antiplatelet, anticoagulant drugs with LMWH preferred

57
58
59 288 6. Subjects can use proton pump inhibitors: omeprazole, pantoprazole, etc
60

- 1
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3
4 289 7. Subjects can use active vitamin D, calcium, phosphorus lowering drugs
5
6 290 8. Subjects can use folic acid, iron, EPO and other anemia drugs with target Hb 100-120g/L
7
8
9 291 9. If diuretics needed, avoid thiazide diuretics
10
11 292 10. Avoid long-term use of corticosteroids (subjects use prednisone <30mg/d, or equivalent
12
13
14 293 amount of other hormones and the use of <2 weeks can be enrolled)
15
16
17 294 11. Avoid using allopurinol, benzbromarone, febuxostat or probenecid
18
19
20 295 12. Avoid long-term use of salicylic acid drugs (except low-dose aspirin), diuretics, losartan)
21
22 296 13. Avoid the use of immunosuppressive agents, such as cyclophosphamide, MMF, CsA,
23
24 297 FK506, azathioprine, vidarabine, leflunomide, Tripterygium glycosides , CD20 antibody,
25
26 298 didanosine.

29 30
31 **Outcomes**

32 300 The primary outcome is cardiovascular events composing of cardiovascular mortality and
33
34 301 non-fatal cardiovascular events, cardiovascular mortality includes deaths caused by acute
35
36 302 myocardial infarction, fatal arrhythmia, sudden death, cardiomyopathy, heart failure, and
37
38 303 stroke; non-fatal cardiovascular events includes non-fatal acute myocardial infarction,
39
40 304 hospital admission of heart failure, unstable angina, atherosclerotic disease needed
41
42 305 hospitalization (including aneurysm, arterial dissection, arteriosclerosis occlusion), non-fatal
43
44 306 stroke, transient ischaemic attack or lower limb ischaemia.

45
46 307 Secondary outcomes include all-cause mortality, cardiovascular mortality and non-fatal
47
48 308 cardiovascular events separately.

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56 309 **Participant timeline**

310 All participants who are eligible and who have signed the informed consent will be
 311 randomized to one of the two treatment groups. Study flowchart was shown in Figure 1.
 312 Treatment in both groups and follow-up will last for another 3 years. Examinations will
 313 involve outpatient appointments in either outpatient clinics or private nephrology practices
 314 and will include: History and physical examination, measurement of systolic and diastolic
 315 arterial blood pressure, recording of the frequency, type, severity and duration of adverse
 316 events as well as laboratory tests including repeated blood counts. Intervals between
 317 examinations vary from monthly (start of study) to 3 monthly (end of study). An overview of
 318 examinations is given and obligatory measurements during the trial are given in table 1.

319 **Table 1 Data collection items and activities by visit during the study period of the LUMINA**

320

Study

	SCREENING PERIOD visit 1 -3 weeks to day 0		visit 2 1st month(m o) (±7d)	visit 3 2nd mo (±7d)	visit 4 3rd mo (±7d)	visit 5 6th mo (±7d)	visits every 3 mo	v15 36 mo
	washout(-3 weeks to -1 week)	Visit 1a(-1 week to day0)						
Physical examination		+		+	+	+	+	+
Blood routine		+		+	+	+	+	+
Urine routine		+		+	+	+	+	+
Uric creatinien		+		+	+	+	+	+
Glycosylated hemoglobin		+				+	+	+
Serum uric acid		+		+	+	+	+	+
Creatinine, potassium, sodium, calcium, phosphorus, bicarbonate, bilirubin, albumin		+		+	+	+	+	+
Parathyroid Hormone		+				+	+	+
Erythropoietin, folic acid, serum feritin, transferrin		+				+	+	+

Serum lipid		+		+	+	+	+	+
24h urine output		+		+	+	+	+	+
Dialysis dose		+		+	+	+	+	+
Kt/V, renal creatinine clearance rate, peritoneal creatinine clearance rate		+		+	+	+	+	+
Peritoneal Equilibrium Test (PET)		+					every 6 mo	+
24h ultrafiltration		+		+	+	+	+	+
Pregnancy test (Female)		+		+	+	+	+	+
Electrocardiograph (ECG)		+				+	+	+
Cardiac ultrasonography and vascular ultrasound		+					every 12mo	+

321 *Note: Treatment in both groups and follow-up will last for another 3 years. In the first 3 months at the
 322 start of study, visit interval will be monthly. After that, visit interval will be three monthly till the end
 323 of study. Examinations will involve outpatient appointments in either outpatient clinics or private
 324 nephrology practices and will include: History and physical examination, measurement of systolic and
 325 diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse
 326 events as well as laboratory tests including repeated blood counts.

327 **Sample size**

328 According to previous studies, 3-year CVD event-free survival was 55% in non-intervening
 329 patients, and 3-year CVD event-free survival was 68% in intervening patients, based on a
 330 power of 80%, with type I error $\alpha=0.05$, two-sided test, and 1:1 parallel control study, a
 331 sample size about 219 cases is estimated. But considered a 20% drop-out rate due to loss of
 332 contact and quitting, it is designed to recruit 274 patients from each group, and a total of 548
 333 patients will be needed. The patients will be assigned randomly into the intervention group or
 334 the control group.

335 **Recruitment**

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4 336 Each center had routine peritoneal dialysis population. These patients were followed up
5
6 337 routinely. Each center will screen subjects to achieve the target population is achieved (548
7
8
9 338 subjects) from these populations. The enrollment period will extend over 24 months.
10
11 339 Research assistants and investigators screen participants from the routine clinical visits. The
12
13
14 340 enrollment period was over 24 months. Up to December 31, 2019, all patients have been
15
16
17 341 enrolled.

18 19 342 *Allocation*

20 21 343 *Sequence generation*

22
23
24 344 To ensure that numbers in the intervention group and the control group equal to each other in
25
26
27 345 each center, stratified randomization method will be used according to the center. And patient
28
29
30 346 will be randomly assigned to one of the two treatments in each center. Allocation sequence
31
32
33 347 was generated by computer-generated random numbers with the help of SAS9.2 software.

34 35 348 *Allocation concealment mechanism*

36
37
38 349 Tablets of febuxostat and placebo will be made and wrapped in the same appearance.
39
40 350 Allocation sequence was generated with the help of SAS9.2 software, When participants were
41
42
43 351 enrolled, investigators would randomly distribute an allocation sequence to the participant
44
45
46 352 using SAS 9.2 software (randomization number), and the corresponding number of study
47
48
49 353 tablets would be distributed to the participants. During these processes, trial participants and
50
51 354 investigators are blinded to the treatment,

52 53 355 *Implementation*

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4 356 Investigators would randomly distribute an allocation sequence to the participant using SAS
5
6 357 9.2 software (randomization number), and the corresponding number of study tablets would
7
8
9 358 be distributed to the participants.
10

11 359 ***Blinding***

12
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14 360 *Who will be blinded and how*

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16
17 361 After assignment to interventions, trial participants, care providers, outcome assessors, data
18
19 362 analysts will be blinded. The placebo and febuxostat will be provided in the same tablet and
20
21 363 the same packaging (including labels) to protect the blindness. Use the kit number to mark
22
23 364 each double-blind treatment. The researchers will obtain the kit number through a random
24
25 365 procedure when patients are randomly grouped, At the same time, during treatment and
26
27 366 follow-up, patients, researchers and research center staff could not obtain which group the
28
29 367 patients were assigned to.
30
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35 368 *Procedure for unblinding if needed*

36
37 369 Blindness can be broken only in order to treat subjects and must know which treatment group
38
39 370 they are randomly assigned to.
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43 371 Blindness can be broken at any time by using the corresponding module of the medical record
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45 372 and/or by calling the sponsor. If the blindness is broken, the researcher should record the date,
46
47 373 time, and cause of the unblindness, and report this information (or "required relevant
48
49 374 information") on the appropriate page of the case report form (CRF).
50
51

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53 375 When recording the causes of unblindness, the researcher must not provide any detailed
54
55 376 information related to the nature of the drug in the study. Until the database is closed, the
56
57 377 researcher shall not disclose the details of the research drug to the sponsor representative or
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4 378 any staff. In addition, when completing forms, research treatments shall not be disclosed in
5
6 379 these tables. After breaking the blindness, the patient must withdraw from the study.
7
8

9 380 ***Data collection methods***

10
11 381 All patients who are eligible and who have signed the informed consent will be randomized to
12
13 382 one of the two treatment groups. Treatment in both groups and follow-up will last for another
14
15 383 3 years. Examinations will involve outpatient appointments in either outpatient clinics or
16
17 384 private nephrology practices and will include: History and physical examination,
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19 385 measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type,
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21 386 severity and duration of adverse events as well as laboratory tests including repeated blood
22
23 387 counts. Intervals between examinations vary from monthly (at the first 3 months at entry of
24
25 388 the study) to 3 monthly (from 3 months after entry to the end of study). An overview of
26
27 389 examinations is given and obligatory measurements during the trial are given in table 1.
28
29
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32
33 390 Baseline characteristic, lab tests and examinations in every visit, adverse events and outcomes
34
35 391 etc will be recorded.
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40 392 ***Plans to promote participant retention and complete follow-up***

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43 393 Participants would be followed up by clinical visits monthly at the first 3 months at entry of
44
45 394 the study and every 3 months thereafter. Research assistants and nurses would follow up the
46
47 395 participants' outcome data and adverse events and reported to the investigators.
48
49

50 396 ***Data management***

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52
53 397 A case report form (CRF) is provided for every study participant, where all information about
54
55 398 examinations and visits have to be recorded. Following the completion of the form, the
56
57 399 original should be sent to the Trial Office and the carbon copy kept by the centre. These
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4 400 carbon copies may be required should the original be lost and for comparison of the patient
5
6 401 data at the end of the study. Documents of the study are subdivided into five categories:
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9 402 recruiting documents, randomization documents, patient books (CRFs), correction documents
10
11 403 and evaluation documents. The pages of the CRFs will be originals with integrated carbon
12
13
14 404 copies. Following the completion of the form, the original should be sent to the Trial Office
15
16
17 405 and the carbon copy kept by the centre. All data will be entered into the database. The
18
19 406 database is developed and administered centrally by the responsible personnel at the institute
20
21
22 407 of medical statistics, but data entry may be achieved in a distributed manner within the trial
23
24
25 408 office. The database will provide online plausibility checks, Log file and backup mechanisms.
26
27 409 Completeness of the patient data and has to be checked. This is supported by plausibility
28
29 410 checks. Double data entry will be conducted. The documentation of the patients will be
30
31
32 411 monitored by the documentation centre. In order to maintain the time course of the follow-up
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34
35 412 examinations of the participants, each physician will receive, after submitting the initial
36
37
38 413 patient documents (recruitment documentation, consent form, medical history and therapy
39
40
41 414 protocol) a list of preferred dates for follow-up examinations. In the documentation centre all
42
43
44 415 patient data will be checked for completeness and plausibility. Should patient documents be
45
46
47 416 incomplete, contain mistakes or be ambiguous, the documentation centre will send a
48
49
50 417 correction form (if necessary with a copy of the incomplete patient documents) to the treating
51
52
53 418 physician. It is required that the treating physician fills in the correction form and returns it to
54
55
56 419 the documentation centre. The execution of each step of the statistical analysis (data
57
58
59 420 modification, data transformation, description of the data, statistical tests) must be logged in a
60 421 protocol by the documentation and statistical centre.

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4 422 ***Statistical methods***

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6 423 ***Statistical methods for primary and secondary outcomes***

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8 424 Descriptive statistics will be used to analyse the means and distribution between all the study
9
10 425 variables. The means of the normal distributed variables will be compared with the student
11
12 426 T-test and non-parametric tests (Mann-Whitney U-test for continued and Chi-Square test for
13
14 427 nominal variables) will be used for the variables that do not follow a normal distribution.
15
16 428 Missing values will be imputed using multiple imputation techniques. Comparisons between
17
18 429 groups will be based on types of variables and appropriate methods in analyses. Kaplan Meier
19
20 430 survival curve will be used to estimate the difference in survival rates between groups, while
21
22 431 Log-rank test and multivariable cox regression will be used to analyze the latter. During the
23
24 432 data-analysis, sensitivity analyses will be conducted by adding an additional covariate in the
25
26 433 mixed model to account for rescue medication required during the study.

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30 434 ***Methods for additional analyses***

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33 435 No applicable.

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36 436 ***Methods in analysis to handle protocol non-adherence and any statistical methods to***

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38
39 437 ***handle missing data***

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41 438 Per-Protocol population (PP) who have protocol adherence between 80%-120%, no serious
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43 439 violation of the protocol, no missing data on the primary outcomes will be included in the
44
45 440 analysis. Multiple imputation will be used to handle missing data.

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49 441 ***Monitoring***

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51 442 ***Composition of the data monitoring committee***

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54 443 No applicable. As this study is funded by our university also, there is a scientific research
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56 444 department who is independent of the investigators and will act as safeguard the interests of

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4 445 trial participants, monitor the main outcome measures including safety and efficacy, and
5
6 446 monitor the overall conduct of the trial.
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9 447 ***Harms***

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11 448 The adverse reactions of febuxostat include liver function damage, allergic reaction such as
12
13 449 systemic skin rash, and acute episode of gout. Study drugs should be stopped if the adverse
14
15 450 reactions occur and proper treatment should be given. All adverse events, whether related to
16
17 451 study drugs or not, should be recorded in detail on the case report form. When the adverse
18
19 452 event is considered not related to study drug, possible reasons should be given. The report of
20
21 453 adverse event should include the following information: name of the adverse event,
22
23 454 occurrence time, end time, study drug information (dose, capacity, treatment date and time or
24
25 455 time interval), severity of the adverse event, the relationship of the adverse event and study
26
27 456 drugs, treatment of the adverse event, and whether it is serious adverse event. Researchers
28
29 457 must track all adverse events until they are resolved or explained by other reasons. Serious
30
31 458 adverse events were defined according to the globally accepted definitions in the International
32
33 459 Conference on Harmonization Guideline for Clinical Safety Data Management. For serious
34
35 460 adverse events, the researchers should fill out the adverse event report form and report them
36
37 461 to the principal investigators, security commissioner, the Ethics Committee Report and China
38
39 462 Food and Drug Administration (CFDA) within 24 hours. Serious adverse events were
40
41 463 recorded from the time the patient consented to be in the study through 30 days after study
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43 464 exit.
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55 465 ***Auditing***

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58 466 Auditing would be conducted every 6 months, the process will be independent from
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4 467 investigators and the sponsor. Representatives of the Sponsor or its designee must be allowed
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6 468 to visit the study center periodically to assess the quality of the data and the integrity of the
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9 469 study. The representatives will review study records at the study center and directly compare
10
11
12 470 these with the source documents, discuss the conduct of the study with the Investigator, and
13
14 471 verify the appropriateness of the conduct of the study. In addition, the study may be evaluated
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16
17 472 by the Sponsor's internal auditors who must be allowed access to eCRFs, source documents,
18
19 473 and other study files. The Sponsor audit reports will be kept confidential.

20
21
22 474 The Investigator or a designated member of the Investigator's staff must be available at some
23
24 475 time during the monitoring visits to review data, resolve any queries, and allow direct access
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26
27 476 to subjects' records (eg, medical records, office charts, hospital charts, and study-related
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29
30 477 charts) for source data verification. The eCRFs must be completed before each visit and be
31
32
33 478 made available to the Sponsor's representative in order that the accuracy and completeness of
34
35 479 the eCRF may be checked.

36 37 38 480 **Ethics and dissemination**

39
40 481 This study has been approved by the Medical Ethics Committee of the First Affiliated
41
42
43 482 Hospital, Sun Yat-sen University and the ethics committees of other participating institutions.
44
45
46 483 The investigators will obtain informed consent or assent from potential trial participants or
47
48 484 authorised surrogates. Investigators will go through all the participants case history and lab
49
50
51 485 tests, and screen participants according to inclusion and exclusion criteria, if participant is
52
53
54 486 eligible to the study, the investigator will talk with the participants and their authorized
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56 487 surrogates about the trial, including time scheme, benefits and risks and so on, and answered
57
58 488 the questions participants have about the trial, after these, investigators obtained written
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60

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4 489 informed consent from the potential trial participants or authorised surrogates.
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7 490 No additional consent provisions for collection and use of participant data and biological
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9 491 specimens in ancillary studies is applicable in this trial.
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13 492 ***Confidentiality***

14
15 493 All subject information, medical records, and laboratory data will be kept
16
17 494 confidential. Information and data may be discussed, analyzed, and reported for the purposes
18
19 495 of this clinical study only. However, code numbers will identify the subject on the eCRFs and
20
21 496 in any reports, and the subject's identity will be kept confidential.
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23

24 497 ***Declaration of interests***

25
26 498 The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China.
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30 499 All authors declared no conflicts of interest.
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33 500 ***Access to data***

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35 501 The datasets used and/or analysed during the current study are available from the
36
37 502 corresponding author on reasonable request.
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40 503 ***Ancillary and post-trial care***

41
42 504 No applicable.
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45 505 ***Dissemination policy***

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47 506 Findings will be disseminated through publications in peer-reviewed journals, and
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49 507 presentations at national and international conferences.
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52 508 **Discussion**

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54 509 Hyperuricemia has been reported to be an independent predictor for cardiovascular outcome
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4 510 in general patients and in CKD patients [7-15]. However, there are limited studies to examine
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6 511 the relationship between serum uric acid levels with cardiovascular mortality in patients on
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9 512 maintenance dialysis. A multicenter observational study from China that included 2264
10
11 513 patients on maintenance PD, with a median follow up of 26.5 months, found that for each
12
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14 514 1mg/dl increase in serum uric acid increase 12% risk in cardiovascular death, and a 5%
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16
17 515 increase in all-cause mortality[4]. From our center, it was found that for each 1mg/dl increase
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20 516 in serum uric acid in male patients, risks of cardiovascular and all-cause mortality increased
21
22 517 by 44% and 33% respectively [27].

23
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25 518 Lowering serum uric acid was demonstrated to benefit renal outcomes [26, 28]. In the
26
27 519 recently published FREED study, febuxostat lowers uric acid and delays the progression of
28
29
30 520 renal dysfunction [29]. However, whether treatment of hyperuricemia could improve their
31
32 521 cardiovascular outcomes in dialysis patients, it is still an imperative topic to be explored.

33
34
35 522 The present LUMINA study is designed to answer this question whether treatment of
36
37 523 hyperuricemia will benefit cardiovascular outcomes in PD patients. It will provide evidence on
38
39
40 524 effect of lowering uric acid on cardiovascular outcomes in PD patients.

41
42
43 525 The LUMINA study has some limitations. Firstly, we recruit prevent and incident patients
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45 526 concurrently, which might have some bias in baseline characteristics. Secondly, since center
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47
48 527 management capability is not parallel in different centers, thus may lead to center bias in the
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50
51 528 study. However, it also has some strength. It is a multicenter, randomized, double blinded and
52
53 529 controlled design, and has sufficient power to detect a clinically significant difference on
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55
56 530 effect of cardiovascular events between treatment and not treatment of hyperuricemia in PD
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58 531 patients.

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4 532 To our knowledge, LUMINA study is the first trial focusing on lowering hyperuricemia
5
6 533 treatment and cardiovascular outcomes in PD patients. Results of this study will provide
7
8
9 534 evidence on whether lowering hyperuricemia treatment is of clinical value in PD patients.
10

11 535 **Acknowledgments**

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13
14 536 The authors acknowledge the participants for their time and their extraordinary commitment
15
16
17 537 to the LUMINA trial. The authors also acknowledge all members of the LUMINA
18
19
20 538 Collaborative Research Group, which includes investigators and staff from 24 clinical centers,
21
22
23 539 the Data Coordinating Center, and the primary sponsor, WanBang Pharmaceutical Marketing
24
25
26 540 and Distribution Co. The 24 clinical centers are The First Affiliated Hospital, Sun Yat-Sen
27
28
29 541 University, The Affiliated Tongji Hospital of Tongji University, The Second Affiliated
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32 542 Hospital of Suzhou University, The Second Xiangya Hospital of Central South University,
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35 543 The Third Xiangya Hospital of Central South University, The First Affiliated Hospital of
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38 544 Xi'an Jiaotong University, The First Hospital of Jilin University, Henan Provincial People's
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41 545 Hospital, The First Affiliated Hospital of Nanchang University, Sichuan Provincial People's
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47 547 Ningxia Medical University, Zhejiang Provincial People's Hospital, Nanjing First Hospital,
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50 548 Pingdingshan First People's Hospital, The First Affiliated Hospital of Zhengzhou University,
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53 549 The Second Hospital of Shanxi Medical University, Xiangya Hospital Central South
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56 550 University, Wuxi Second People's Hospital, Chenzhou No.1 People's Hospital, Shengjing
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59 551 Hospital of China Medical University, Yancheng City No.1 People's Hospital, The First
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62 552 People's Hospital of Kunshan, Zhenjiang First People's Hospital.

63 553 **Disclosure and conflicts of interest**

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555 All authors declared no conflicts of interest.

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557 **Figure 1. Study flow chart**

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BMJ Open

The rationale and design for Lowering-hyperUricemia treatment on cardiovascular outcomes in peritoneal dialysis patients: a prospective, multicentre, double-blind, randomized controlled trial (LUMINA)

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1 **The rationale and design for Lowering-hyperUricemia treatment on**
2 **cardiovascular outcoMes In peritoNeal diAlysis patients: a prospective,**
3 **multicentre, double-blind, randomized controlled trial (LUMINA)**

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28 **Word counts:** 4439 words.

29 **Keywords:** Hyperuricemia, cardiovascular outcomes, peritoneal dialysis

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4 **31 Abstract**

5
6 **32 Introduction**

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8
9 33 The prevalence of hyperuricemia in peritoneal dialysis patients is quite high. Studies have
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11 34 demonstrated a correlation between hyperuricemia and cardiovascular disease and treatment
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14 35 of hyperuricemia reportedly reduces cardiovascular risk in chronic kidney disease (CKD)
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17 36 patients. However, whether hyperuricemia treatment benefits cardiovascular outcomes in
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19
20 37 continuous ambulatory peritoneal dialysis (CAPD) patients is not yet known.

21
22 **38 Methods and analyses**

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25 39 This prospective, multicentre, double-blind, randomized controlled trial was designed to
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28 40 evaluate the effects of hyperuricemia treatment on cardiovascular event risk in CAPD
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31 41 patients. Based on a power of 80%, with type I error $\alpha=0.05$, two-sided test, and 1:1 parallel
32
33
34 42 control study, considering a dropout rate of 20%, a total of 548 eligible patients are expected
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36
37 43 to be randomly assigned to either the hyperuricemia treatment group (febuxostat) or control
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40 44 group (placebo).

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42 **45 Ethics and dissemination**

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44 46 This study has been approved by the Medical Ethics Committee of the First Affiliated
45
46
47 47 Hospital, Sun Yat-sen University and the ethics committees of other participating institutions.

48
49 48 Written informed consent will be obtained from potential trial participants or authorised
50
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52 49 surrogates.

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54 50 The findings of the study will be disseminated through publications in peer-reviewed journals,
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56
57 51 and presentations at national and international conferences.

58
59 **52 Trial Registration:** ClinicalTrials.gov
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4 53 **Trial number:** NCT03200210

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6 54 **Registered:** 25 June, 2017

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9 55 The trial was started on July 13, 2017, and is expected to end by December 31, 2022. Till Jan
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11 56 20, 2020, a total of 548 patients have been recruited.

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15 16 17 58 **Strengths and limitations of this study**

18
19 59 1. To our knowledge, this is the first large sample size randomized clinical trial to evaluate
20
21 60 whether high uric acid level is a potentially modifiable risk factor for cardiovascular mortality
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23 61 in peritoneal dialysis patients.

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27 62 2. This is a prospective, multicentre, double-blind, randomized controlled trial powerful
28
29 63 enough to test the hypothesis.

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31
32 64 3. The LUMINA study has some limitations. First, we recruit prevalent and incident patients
33
34 65 concurrently, which might create some bias in baseline characteristics

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36
37 66 4. Secondly, since centre management capability is not parallel across different centres, to the
38
39 67 potential centre bias exists in this study.

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43 44 45 69 **Protocol version**

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48 70 The protocol version number and date are YLT-1604-V2.0, December 15, 2016,

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52
53 72 The work was sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China,
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6 76 Guangzhou, China (2002B60118), 5010 Clinical Program of Sun Yat-sen University
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18
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30 85 Drs. Wei Chen and Naya Huang contributed equally to this work.

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32 86 Contributions:

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35 87 All authors have made substantial contributions to this work. Contributions of the authors are
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44 91 Formal analysis: Qian Zhou, Naya Huang

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47
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49
50 94 Methodology: Naya Huang, Wei Chen, Qian Zhou, Jun Ding

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52 95 Project administration: Wei Chen, Xueqing Yu

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54 96 Resources: Xueqing Yu, Jun Ding

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6 98 Supervision: Xueqing Yu
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9 99 Validation: Wei Chen, Xueqing Yu
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12
13

14 101 Roles/Writing - original draft: Naya Huang, Wei Chen
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4 141 The sponsor participated in the design of the study, but had no role in the collection,
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6 142 management, analysis or interpretation of data, writing of the report, or the decision to submit
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9 143 the report for publication.
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11 144 ***Composition, roles, and responsibilities of the coordinating centre, steering committee,***
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14 145 ***endpoint adjudication committee, data management team, and other individuals or groups***
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17 146 ***overseeing the trial, if applicable (see Item 21a for data monitoring committee)***
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19 147 Not applicable.
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24 149 **Introduction**

25 150 ***Background and study rationale***

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27 151 Elevated serum uric acid (SUA) seen in patients with chronic kidney disease (CKD), partly
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30 152 arises from overproduction of purines due to hypercatabolism, as well as reduced excretion of
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33 153 uric acid by the kidneys. It previously was shown that there was a correlation between higher
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36 154 uric acid levels and lower glomerular filtration rate (GFR) [1-3]. Hyperuricemia is common in
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39 155 the general population with a prevalence of 13.3-42.1% [4-6]. Based on an epidemiological
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42 156 study in Southern China, the prevalence of hyperuricemia in the adult population is as high as
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45 157 31.9% [6]. Reduced GFR is seen in CKD patients and understandably conveys a higher
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48 158 prevalence of hyperuricemia than in the general population. Our local data revealed that the
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51 159 prevalence of hyperuricemia at our peritoneal dialysis (PD) center is 63.1% [6].
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53 160 Many epidemiologic and clinical studies have demonstrated a correlation between
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56 161 hyperuricemia and cardiovascular diseases [7-15]. The literature also suggests hyperuricemia
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59 162 is associated with other classical cardiovascular risk factors, such as hypertension [16],
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4 163 diabetes mellitus [17], hyperlipidaemia [18], obesity and insulin resistance [19, 20]. Evidence
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6 164 shows that elevated in serum uric acid levels facilitate the oxidation of low density lipoprotein
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9 165 cholesterol [18], and hyperuricemia is accompanied by increased free oxygen radical
10
11 166 production, which plays a role in inflammation [21]. Furthermore, elevated uric acid levels
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14 167 facilitate platelet aggregation, increasing the risk for arterial thrombus formation [22]. These
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17 168 features contribute to a higher risk of cardiovascular events.

18
19 169 Treatment of hyperuricemia reportedly independently reduces renal disease progression in
20
21
22 170 CKD patients [23, 24], and treatment of hyperuricemia was associated with reduced mortality
23
24
25 171 among haemodialysis (HD) patients with no history of cardiovascular disease (CVD) in the
26
27 172 Dialysis Outcomes and Practice Patterns Study (DOPPS) study in Japan [25]. Additionally, in
28
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30 173 CKD patients, treatment of hyperuricemia has been shown to reduce cardiovascular risk [26].
31
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33 174 However, whether treatment that lowers uric acid would benefit cardiovascular outcomes in
34
35 175 CKD patients, especially in maintenance dialysis patients, is not yet known.

36 37 38 176 **Objectives**

39
40 177 To investigate whether hyperuricemia-lowering therapy through use of febuxostat reduces the
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43 178 risk of cardiovascular events in CAPD patients.

44 45 179 **Trial design**

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47
48 180 The study is a prospective, multicentre, double-blind, randomized controlled trial.

49 50 181 **Methods**

51 52 182 **Study setting**

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55 183 The study is being conducted in mainland China across 24 academic hospitals. A complete
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57
58 184 list of study sites is given in the acknowledgements.
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4 185 ***Inclusion criteria:***

- 5
6 186 1. Subjects who are able to understand and have voluntarily signed the informed consent form
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9 187 (ICF)
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11 188 2. Adults aged 18-70 at the time of randomization
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13 189 3. Subjects on PD for longer than 3 months
14
15 190 4. Subjects with hyperuricemia defined as follows: female: 6mg/dl(360µmol/L)
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20 191 <sUA<12mg/dl(720µmol/L); male: 7mg/dl(420µmol/L) <sUA<12mg/dl(720µmol/L)
21

22 192 ***Exclusion criteria:***

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24 193 1. Subjects who have a history of gout
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26 194 2. Subjects who have a myocardial infarction, unstable angina, cardiovascular reconstructive
27
28 195 surgery (such as a stent or bypass surgery), cerebrovascular accident 12 weeks prior to
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30 196 randomization, or planned cardiovascular reconstructive surgery during the trial
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33 197 3. Subjects who have New York stage IV heart failure within 4 weeks prior to screening
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36 198 4. Subjects who have previously received kidney transplantation and are currently prescribed
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38 199 immunosuppressive therapy
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41 200 5. Subjects who have severe liver disease, such as acute hepatitis, chronic active hepatitis,
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44 201 cirrhosis
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47 202 6. Subjects who have alanine aminotransferase (ALT) levels greater than 2 folds the upper
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49 203 limit of normal or total bilirubin greater than 1.5 folds the upper limit of normal
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52 204 7. Subjects who have experienced severe infections within 4 weeks prior to the screening,
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55 205 such as pneumonia or peritoneal dialysis-related peritonitis;
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4 206 8. Subjects who have had a major surgery within 12 weeks prior to screening or who are not
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7 207 yet fully recovered from surgery
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9 208 9. Subjects who have a malignancy
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12 209 10. Subjects who report a history of illicit drug use or a regular or daily alcohol consumption
13
14 210 of ≥ 4 alcoholic drinks per day in the 2 years prior to screening
15
16
17 211 11. Subjects who are allergic to febuxostat
18
19
20 212 12. Subjects who are enrolled in other clinical studies within 4 weeks prior to or at
21
22 213 randomization
23
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25 214 13. Subjects who are currently taking mercaptopurine, azathioprine, vidarabine or didanosine
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28 215 14. Subjects who are taking losartan, fenofibrate, thiazide diuretics or loop diuretics within 4
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30 216 weeks of randomization
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33 217 15. Subjects who require long-term use of steroids (prednisone $<30\text{mg/d}$, or equivalent
34
35 218 amount of other steroids and use of <2 weeks can be enrolled)
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38 219 16. Subjects who require long-term use of salicylic acid drugs except low-dose aspirin
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41 220 17. Fertile, lactating patients who are unwilling or unable to take contraceptives
42

43 221 ***Patient and Public Involvement***

44
45 222 We state that neither patients nor the public WERE involved in the design, conduct, reporting,
46
47
48 223 or dissemination plans of our research.
49

50 224 ***Interventions***

51
52
53 225 Eligible patients will be randomly assigned to the febuxostat treatment group or the placebo
54
55
56 226 control group
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58 227 ***Dose adjustment***

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4 228 Participants are treated with febuxostat/placebo starting at a dose of 20mg /day, once a day. If
5
6 229 SUA does not reach the target level (SUA<6mg/dl) or decreases less than 20% at the 4-week
7
8
9 230 visit, the dosage is increased to 40mg/d once per day. If SUA does not reach target at the
10
11 231 8-week visit, the dosage is increased to 40mg/day (for those who are at dosage of 20mg/day)
12
13
14 232 or the dosage is maintained (for those who are at dosage of 40mg/day) until the end of the
15
16 233 study. If at dosage of 40mg/d and SUA remains >12mg/dl for 2 weeks, patients are withdrawn
17
18 234 from the study for their safety. If SUA reaches <3mg/dl at dose of 40mg/d, the dose decreased
19
20 235 to 20mg/d, and SUA is checked 2 weeks later. At that time, if SUA is still <3mg/dl, treatment
21
22 236 is stopped for 2 weeks, and SUA is checked again, if SUA still <3mg/dl, patients are
23
24 237 withdrawn from the study. if SUA is \geq 3mg/dl, the 20mg/d dose is maintained, until SUA is
25
26 238 above the target level (\geq 6mg/dl), at which point the dose is increased to 40mg/d.
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33 239 ***Criteria for discontinuing or modifying allocated interventions***

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35 240 1. Subjects with continued withdrawal of more than 2 weeks or intermittently stopping more
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37 241 than one month
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40 242 2. Subjects who experience intolerable side effects
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43 243 3. For subjects who have episodes of gout, if SUA remains <6mg/dl, patients are kept in the
44
45 244 trial after acute treatment; however, if SUA \geq 6mg/dl, patient allocation is unblinded,
46
47 245 hyperuricemia is treated, and patients are withdrawn from the trial
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50 246 4. Subjects who have no evaluable records available
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53 247 5. Subjects who have to use prohibited medications due to illness
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4 248 6. Subjects who have ALT, or AST increases to greater than 2 times of upper limit of normal
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6 249 or elevated bilirubin to more than 2 times the upper limit of normal that has been persistently
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9 250 elevated for 2 weeks
10
11 251 7. Subjects who have SUA > 12 mg/dl for 2 weeks who are on the maximum treatment dose
12
13
14 252 8. Subjects who have SUA < 12 mg/dl for 4 weeks who are on the minimal dose of treatment
15
16
17 253 9. Subjects who have adverse events and cannot continue the study
18
19
20 254 10. Subjects who have unexplained complications
21
22 255 11. Subjects who become pregnant during treatment
23
24
25 256 12. Subjects who have kidney transplantations during the study
26
27 257 13. If, for safety reasons, the organizers propose to stop the study
28
29
30 258 14. If the Ethics Committee decides to discontinue the study
31
32
33 259 15. If the research is considered unsuitable for continued research subjects

34
35 260 The investigator may terminate a subject's study participation at any time during the study
36
37 261 based on the subject's best interest. In addition, a subject may discontinue his or her
38
39 262 participation at any time during the study.

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43 263 ***Strategies to improve adherence to interventions***

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45 264 Participants will be followed up monthly during the first 3 months of the study and every 3
46
47 265 months thereafter until the end of the study. Examinations involve outpatient appointments in
48
49 266 either outpatient clinics or private nephrology practices and will include: history and physical
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51 267 examination, measurement of systolic and diastolic arterial blood pressure, recording of the
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53 268 frequency, type, severity and duration of adverse events as well as laboratory tests that
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56 269 include repeated blood counts.
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4 270 ***Relevant concomitant care permitted or prohibited during the trial***

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6 271 Medications to treat concomitant conditions are allowed and are recorded at baseline and each
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8
9 272 follow-up visit. Participants are encouraged to remain on the same dosage of these
10
11 273 medications unless advised otherwise by medical professionals. Participants who used
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14 274 diuretics, losartan should be asked to discontinue use for 2 weeks before screening, and
15
16
17 275 patients who used prednisone ≥ 30 mg/d for more than 2 weeks and other drugs that treat
18
19 276 hyperuricemia other than the assigned trial medications are considered to have dropped out of
20
21
22 277 the trial.

23
24
25 278 ***Relevant concomitant care permitted or prohibited during the trial***

- 26
27 279 1. If taking ACEI/ARB before the trial, patients can continue but are not to increase the dose
28
29 280 during the trial; however, the need to avoid the use of losartan. If patients are not taking
30
31 281 ACEI/ARB at the time of enrolment, it is not to be added during the study.
- 32
33 282 2. If SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, the dosages of other anti-hypertension drugs are to
34
35 283 be adjusted, except for ACEI/ARB.
- 36
37 284 3. Lipid-lowering drugs can be used during the study, including statins to treat high
38
39 285 cholesterol and fibrates to treat hypertriglyceridemia primarily to maintain normal cholesterol,
40
41 286 triglycerides, and low-density lipoprotein levels.
- 42
43 287 4. Anti-glycaemic drugs can be used, such as insulin, to reach target glycaemia control with
44
45 288 HbA1c $< 7.0\%$
- 46
47 289 5. Subjects can use antiplatelet and anticoagulant drugs with LMWH preferred.
- 48
49 290 6. Subjects can use proton pump inhibitors, such as omeprazole, pantoprazole, etc.
- 50
51 291 7. Subjects can use active vitamin D, calcium, and phosphorus lowering drugs.
- 52
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4 292 8. Subjects can use folic acid, iron, EPO and other anaemia drugs with target Hb of

5
6 293 100-120g/L

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8
9 294 9. If diuretics are needed, patients should avoid thiazide diuretics

10
11 295 10. Avoid long-term use of corticosteroids (subjects using prednisone <30mg/d, or equivalent

12
13
14 296 number of other hormones with use of <2 weeks can be enrolled).

15
16
17 297 11. Avoid using allopurinol, benzbromarone, febuxostat or probenecid.

18
19 298 12. Avoid long-term use of salicylic acid drugs (except low-dose aspirin), diuretics, and

20
21
22 299 losartan.

23
24 300 13. Avoid use of immunosuppressive agents, such as cyclophosphamide, MMF, CsA, FK506,

25
26
27 301 azathioprine, vidarabine, leflunomide, tripterygium glycosides, CD20 antibody, and

28
29
30 302 didanosine.

31
32 303 ***Outcomes***

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34
35 304 The primary outcome is cardiovascular events comprising cardiovascular mortality and

36
37 305 non-fatal cardiovascular events. Cardiovascular mortality includes death caused by acute

38
39
40 306 myocardial infarction, fatal arrhythmia, sudden death, cardiomyopathy, heart failure, and

41
42
43 307 stroke, while non-fatal cardiovascular events includes non-fatal acute myocardial infarction,

44
45
46 308 hospital admission for heart failure, unstable angina, atherosclerotic disease requiring

47
48
49 309 hospitalization (including aneurysm, arterial dissection, arteriosclerosis occlusion), non-fatal

50
51 310 stroke, transient ischaemic attack or lower limb ischaemia.

52
53 311 Secondary outcomes include all-cause mortality, cardiovascular mortality and non-fatal

54
55
56 312 cardiovascular events separately.

57
58 313 ***Participant timeline***

314 All participants who are eligible and who have signed the informed consent will be
 315 randomized to one of the two treatment groups. A study flowchart was shown in Figure 1.
 316 Treatment in both groups and follow-up will last for 3 years. Examinations will involve
 317 outpatient appointments in either outpatient clinics or private nephrology practices and will
 318 include: history and physical examination, measurement of systolic and diastolic arterial
 319 blood pressure, recording of the frequency, type, severity and duration of adverse events as
 320 well as laboratory tests including repeated blood counts. Intervals between examinations vary
 321 from monthly (start of study) to 3 months (end of study). An overview of examinations is
 322 given and obligatory measurements during the trial are shown in Table 1.

323 **Table 1 Data collection items and activities by visit during the study period for LUMINA**

	SCREENING PERIOD visit 1 -3 weeks to day 0		visit 2 1st month(m o) (±7d)	visit 3 2nd mo (±7d)	visit 4 3rd mo (±7d)	visit 5 6th mo (±7d)	visits every 3 mo	v15 36 mo
	Washout (-3weeks to -1week)	Visit 1a (-1 week to day0)						
Physical examination		+		+	+	+	+	+
Blood routine		+		+	+	+	+	+
Urine routine		+		+	+	+	+	+
Uric creatinine		+		+	+	+	+	+
Glycosylated haemoglobin		+				+	+	+
Serum uric acid		+		+	+	+	+	+
Creatinine, potassium, sodium, calcium, phosphorus, bicarbonate, bilirubin, albumin		+		+	+	+	+	+
Parathyroid Hormone		+				+	+	+
Erythropoietin, folic acid, serum ferritin, transferrin		+				+	+	+
Serum lipid		+		+	+	+	+	+
24h urine output		+		+	+	+	+	+
Dialysis dose		+		+	+	+	+	+

Kt/V, renal creatinine clearance rate, peritoneal creatinine clearance rate		+			+	+	+	+	+
Peritoneal Equilibrium Test (PET)		+						every 6 mo	+
24h ultrafiltration		+			+	+	+	+	+
Pregnancy test (Female)		+			+	+	+	+	+
Electrocardiograph (ECG)		+					+	+	+
Cardiac ultrasonography and vascular ultrasound		+						every 12mo	+

*Note: Treatment in both groups and follow-up will last for another 3 years. In the first 3 months at the start of the study, visit intervals will be monthly. After that, visit intervals will be every three months until the end of study. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts.

330 **Sample size**

331 According to previous studies, 3-year CVD event-free survival is 55% in untreated patients
 332 and 68% in treated patients; therefore, based on a power of 80%, type I error $\alpha=0.05$,
 333 two-sided test, and 1:1 parallel control study, a sample size of approximately 219 cases is
 334 estimated. But considering a 20% drop-out rate due to loss of contact and quitting, this study
 335 was designed to recruit 274 patients from each group, for a total of 548 patients. Patients will
 336 be randomly assigned into the intervention or control group.

337 **Recruitment**

338 Each centre has a routine peritoneal dialysis population, and these patients are followed up
 339 routinely. Each centre will screen subjects to ensure the target population is achieved (548
 340 subjects) from these patients. The enrollment period will last 24 months. Research assistants

1
2
3
4 341 and investigators screen participants from routine clinical visits. The enrolment period has
5
6 342 ended, and as of December 31, 2019, all patients had been enrolled.
7
8

9 343 ***Allocation***

10
11 344 *Sequence generation*

12
13
14 345 To ensure that numbers in the intervention and the control groups were equal in each centre, a
15
16
17 346 stratified randomization method will be used for each centre, and patients will be randomly
18
19 347 assigned to one of the two treatment groups at each centre. The allocation sequence was
20
21
22 348 attained using computer-generated random numbers using SAS9.2 software.
23

24 349 *Allocation concealment mechanism*

25
26
27 350 Tablets of febuxostat and placebo will be made and wrapped to appear the same. The
28
29
30 351 allocation sequence was generated using SAS9.2 software. When participants were enrolled,
31
32 352 investigators randomly distributed an allocation sequence to the participant using SAS 9.2
33
34
35 353 software (randomization number), and study tablet with the corresponding number would be
36
37 354 distributed to the participants. During these processes, both trial participants and investigators
38
39
40 355 are blinded to the treatment,
41

42
43 356 *Implementation*

44
45 357 Investigators randomly distribute an allocation sequence to a given participant using SAS 9.2
46
47
48 358 software (randomization number), and study tablets with the corresponding number are then
49
50
51 359 distributed to the participants.
52

53 360 ***Blinding***

54
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56 361 *Who will be blinded and how*
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4 362 After assignment to interventions, trial participants, care providers, outcome assessors, and
5
6 363 data analysts are blinded. The placebo and febuxostat will be provided in the same tablet and
7
8
9 364 the same packaging (including labels) to protect the blindness, using kit numbers to mark
10
11 365 each double-blind treatment. Researchers will obtain the kit number through a random
12
13
14 366 procedure when patients are randomly grouped, At the same time, during treatment and
15
16
17 367 follow-up, patients, researchers and research centre staff are unable to identify to which group
18
19 368 the patients were assigned.

21
22 369 *Procedure for unblinding if needed*

23
24 370 Blindness can only be broken only to treat subjects when a need to know which treatment
25
26 371 group they are randomly assigned to arises.

27
28
29 372 Blindness can be broken at any time using the corresponding module of the medical record
30
31 373 and/or by calling the sponsor. If blindness is broken, the researcher should record the date,
32
33 374 time, and cause of the unblind, and report this information (or "required relevant
34
35 375 information") on the appropriate page of the case report form (CRF).

36
37
38 376 When recording causes of unblinding, the researcher must not provide any detailed
39
40 377 information related to the nature of the drug in the study. Until the database is closed, the
41
42 378 researcher shall not disclose the details of the research drug to the sponsor representative or
43
44 379 any staff. In addition, when completing forms, research treatments shall not be disclosed in
45
46 380 these tables. After breaking the blinding, the patient must withdraw from the study.

47
48 381 ***Data collection methods***

49
50 382 All patients who are eligible and who have signed the informed consent will be randomized to
51
52 383 one of the two treatment groups. Treatment in both groups and follow-up will last for another
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4 384 3 years. Examinations will involve outpatient appointments in either outpatient clinics or
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6 385 private nephrology practices and will include: history and physical examination, measurement
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8
9 386 of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and
10
11 387 duration of adverse events as well as laboratory tests including repeated blood counts.
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13
14 388 Intervals between examinations vary from monthly (during the first 3 months of the study) to
15
16 389 every 3 months (from 3 months after entry to the end of study). An overview of examinations
17
18 390 is given along with obligatory measurements during the trial in Table 1. Baseline
19
20 391 characteristics, lab tests and examinations in every visit, adverse events and outcomes etc.
21
22 392 will be recorded.
23
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26

27 393 *Plans to promote participant retention and complete follow-up*

28
29
30 394 Participants will be followed up by monthly clinical visit during the first 3 months of the
31
32 395 study and every 3 months thereafter. Research assistants and nurses will follow up
33
34 396 participants outcome data and adverse events, which are reported to the investigators.
35
36

37 397 ***Data management***

38
39
40 398 A case report form (CRF) is provided for every study participant, where all information
41
42 399 concerning examinations and visits are recorded. Following completion of the form, the
43
44 400 original is sent to the Trial Office, and a carbon copy is retained by the centre. These carbon
45
46 401 copies may be required should the original be lost and for comparison of patient data at the
47
48 402 end of the study. Study documents are subdivided into five categories: recruiting documents,
49
50 403 randomization documents, patient books (CRFs), correction documents and evaluation
51
52 404 documents. The pages of the CRFs will be originals with integrated carbon copies. Following
53
54 405 completion of the form, the original will be sent to the trial office, and a carbon copy is
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4 406 retained by the center. All data will be entered into the database. The database is developed
5
6 407 and administered centrally by the responsible personnel at the institute of medical statistics,
7
8
9 408 but data entry maybe achieved in a distributed manner within the trial office. The database
10
11 409 will provide online plausibility checks, log files and backup mechanisms. Completeness of
12
13
14 410 patient data has to be verified. This is supported by plausibility checks. Double data entry will
15
16
17 411 be conducted. Documentation of patients will be monitored by the documentation centre. To
18
19
20 412 maintain the time course of the follow-up examinations of the participants, each physician
21
22 413 will receive, a list of preferred dates for follow-up examinations after submitting the initial
23
24
25 414 patient documents (recruitment documentation, consent form, medical history and therapy
26
27 415 protocol). In the documentation centre, all patient data will be verified for completeness and
28
29
30 416 plausibility. Should patient documents be incomplete, contain mistakes or be ambiguous, the
31
32 417 documentation centre will send a correction form (if necessary, with a copy of the incomplete
33
34
35 418 patient documents) to the treating physician. It is required that the treating physician fills in
36
37 419 the correction form and returns it to the documentation centre. Execution of each step of
38
39
40 420 statistical analysis (data modification, data transformation, description of the data, statistical
41
42
43 421 tests) must be logged in a protocol by the documentation and statistical centre.

422 ***Statistical methods***

423 *Statistical methods for primary and secondary outcomes*

424 Descriptive statistics will be used to analyse the means and distribution between all study
425 variables. The means of the normal distributed variables will be compared to the Student's
426 T-test, and non-parametric tests (Mann-Whitney U-test for continuous and Chi-Square test for
427 nominal variables) will be used for variables that do not follow a normal distribution. Missing
428 values will be imputed using multiple imputation techniques. Comparisons between groups

1
2
3 429 will be based on types of variables and appropriate methods in analyses. A Kaplan Meier
4
5 430 survival curve will be used to estimate difference in survival rates between the groups, while
6
7 431 Log-rank test and multivariable Cox regression will be used to analyse the latter. During
8
9 432 data-analysis, sensitivity analyses will be conducted by adding an additional covariate in the
10
11 433 mixed model to account for rescue medication required during the study.

12
13
14 434 ***Methods for additional analyses***

15
16
17 435 Not applicable.

18
19 436 ***Methods in analysis to handle protocol non-adherence and any statistical methods to***
20
21
22 437 ***handle missing data***

23
24
25 438 Per-Protocol population (PP) that have protocol adherence between 80%-120%, no serious
26
27 439 violation of the protocol, and no missing data on primary outcomes will be included in the
28
29 440 analysis. Multiple imputation will be used to handle missing data.

30
31
32 441 ***Monitoring***

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34
35 442 ***Composition of the data monitoring committee***

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37
38 443 Not applicable. As this study is funded by our university, there is a scientific research
39
40 444 department that is independent of the investigators and will act as a monitoring committee,
41
42 445 safeguard the interests of trial participants, monitor the primary outcome measures including
43
44 446 safety and efficacy, and monitor the overall conduct of the trial.

45
46
47 447 ***Interim analyses and stopping guidelines***

48
49
50 448 Not applicable.

51
52
53 449 ***Harms***

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56 450 Adverse reactions to febuxostat include liver function damage, allergic reactions such as
57
58 451 systemic skin rash, and acute episodes of gout. Study drugs should be stopped if adverse
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4 452 reactions occur and proper treatment should be administered. All adverse events, whether
5
6 453 related to study drugs or not, are recorded in detail on the case report forms. When the
7
8
9 454 adverse event is considered not related to study drug, possible reasons are given. Reporting of
10
11 455 adverse events should include the following information: name of the adverse event,
12
13
14 456 occurrence time, end time, study drug information (dose, capacity, treatment date and time or
15
16
17 457 time interval), severity of the adverse event, relationship of the adverse event to study drug,
18
19 458 treatment of the adverse event, and whether it is a serious adverse event. Researchers must
20
21
22 459 track all adverse events until they are resolved or explained by other reasons. Serious adverse
23
24
25 460 events are defined according to globally accepted definitions in the International Conference
26
27 461 on Harmonization Guideline for Clinical Safety Data Management. For serious adverse
28
29
30 462 events, researchers should fill out the adverse event report form and report them to the
31
32
33 463 principal investigators, security commissioner, and the Ethics Committee Report and China
34
35 464 Food and Drug Administration (CFDA) within 24 hours. Serious adverse events are recorded
36
37
38 465 from the time the patient consent to be in the study through 30 days after study exit.

466 ***Auditing***

467 Auditing will be conducted every 6 months; and the process will be independent from
468 investigators and the sponsor. Representatives of the sponsor or its designee must be allowed
469 to visit the study centre periodically to assess the quality of the data and the integrity of the
470 study. Representatives will review study records at the study centre and directly compare
471 these with the source documents, discuss the conduct of the study with the investigator, and
472 verify the appropriateness of the conduct of the study. In addition, the study may be evaluated
473 by the sponsor's internal auditors who must be allowed access to eCRFs, source documents,

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4 474 and other study files. The sponsor audit reports will be kept confidential.
5
6 475 The investigator or a designated member of the investigator's staff must be available at some
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9 476 time during the monitoring visits to review data, resolve any queries, and allow direct access
10
11 477 to subjects' records (eg, medical records, office charts, hospital charts, and study-related
12
13 478 charts) for source data verification. eCRFs must be completed before each visit and be made
14
15 479 available to the sponsor's representative to ensure that the accuracy and completeness of the
16
17 480 eCRF.

481 **Ethics and dissemination**

482 This study has been approved by the Medical Ethics Committee of the First Affiliated
483 Hospital, Sun Yat-sen University and the ethics committees of other participating institutions.

484 Any amendments to the protocol should be reported to the Medical Ethics Committee.

485 Investigators will obtain informed consent or assent from potential trial participants or
486 authorized surrogates. Investigators will go through all the participants case histories and lab
487 tests, and screen participants according to inclusion and exclusion criteria. If the potential
488 participant is eligible for the study, the investigator will talk with the participants and their
489 authorized surrogates about the trial, including the time scheme, benefits and risks and so on,
490 to answer questions participants have about the trial. After this, investigators obtained written
491 informed consent from the potential trial participants or their authorized surrogates.

492 No additional consent provisions for collection or use of participant data and biological
493 specimens in ancillary studies is applicable in this trial.

494 ***Confidentiality***

1
2
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4 495 All subject information, medical records, and laboratory data will be kept confidential.
5
6 496 Information and data may be discussed, analyzed, and reported for the purposes of this
7
8
9 497 clinical study only. However, code numbers will identify subject on the eCRFs and in any
10
11
12 498 reports, to keep the subject's identity confidential.

13
14 499 ***Declaration of interests***

15
16
17 500 This work is sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China.
18
19 501 All authors declare no conflicts of interest.

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21
22 502 ***Access to data***

23
24 503 The datasets used and/or analysed during the current study are available from the
25
26
27 504 corresponding author on reasonable request.

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30 505 ***Ancillary and post-trial care***

31
32 506 Not applicable.

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35 507 ***Dissemination policy***

36
37 508 Findings will be disseminated through publications in peer-reviewed journals, and
38
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40 509 presentations at national and international conferences. Authorship eligibility guidelines and
41
42
43 510 any intended use of professional writers, plans of granting public access to the full protocol,
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45
46 511 participant-level dataset, and statistical code is not yet available.

47
48 512 **Discussion**

49
50 513 Hyperuricemia is reportedly an independent predictor for cardiovascular outcome in both
51
52
53 514 general and CKD patients [7-15]. However, there are limited studies examining the
54
55
56 515 relationship between serum uric acid levels and cardiovascular mortality in patients on
57
58
59 516 maintenance dialysis. A multicentre observational study from China that included 2,264
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4 517 patients on maintenance PD, with a median follow up of 26.5 months, found that each 1mg/dl
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6 518 increase in serum uric acid caused a corresponding 12% increased risk of cardiovascular
7
8
9 519 death, and a 5% increase in all-cause mortality [4]. From our centre, each 1mg/dl increase in
10
11 520 serum uric acid in male patients, corresponded to increasing the risks of cardiovascular and
12
13
14 521 all-cause mortality by 44% and 33% respectively [27].

15
16
17 522 Lowering serum uric acid was demonstrated to benefit renal outcomes [26, 28]. In the
18
19 523 recently published FREED study, febuxostat lowered uric acid and delayed the progression of
20
21 524 renal dysfunction [29]. However, whether treatment of hyperuricemia improves
22
23 525 cardiovascular outcomes in dialysis patients remains to be explored.

24
25
26
27 526 The present LUMINA study is designed to determine this question whether treatment of
28
29 527 hyperuricemia benefits cardiovascular outcomes in PD patients. It will provide evidence for
30
31 528 the effect of lowering uric acid on cardiovascular outcomes in PD patients.

32
33
34
35 529 The LUMINA study has some limitations. First, we recruit preventative and incidental
36
37 530 patients concurrently, which might introduce some bias in baseline characteristics. Secondly,
38
39 531 since centre management capability is not parallel across different centres, centre bias may be
40
41 532 present in the study. However, this study also has some strengths. This is a multicentre,
42
43 533 randomized, double blind and controlled design with sufficient power to detect a clinically
44
45 534 significant difference on the effect of cardiovascular events between treatment and not
46
47 535 treatment of hyperuricemia in PD patients.

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51 536 To our knowledge, the LUMINA study is the first trial focusing on treatment to reduce
52
53 537 hyperuricemia and its relationship to cardiovascular outcomes in PD patients. Results of this
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4 538 study will provide evidence on whether hyperuricemia-lowering treatment is of clinically
5
6 539 valuable in PD patients.
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9 540 **Acknowledgments**

10
11 541 The authors acknowledge the participants for their time and their extraordinary commitment
12
13 542 to the LUMINA trial. The authors also acknowledge all members of the LUMINA
14
15 543 Collaborative Research Group, which includes investigators and staff from 24 clinical centres,
16
17 544 the Data Coordinating Center, and the primary sponsor, Wanbang Pharmaceutical Marketing
18
19 545 and Distribution Co. The 24 clinical centres are The First Affiliated Hospital, Sun Yat-Sen
20
21 546 University, The Affiliated Tongji Hospital of Tongji University, The Second Affiliated
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23 547 Hospital of Suzhou University, The Second Xiangya Hospital of Central South University,
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25 548 The Third Xiangya Hospital of Central South University, The First Affiliated Hospital of
26
27 549 Xi'an Jiaotong University, The First Hospital of Jilin University, Henan Provincial People's
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29 550 Hospital, The First Affiliated Hospital of Nanchang University, Sichuan Provincial People's
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31 551 Hospital, The First Affiliated Hospital of Guangxi Medical University, General Hospital of
32
33 552 Ningxia Medical University, Zhejiang Provincial People's Hospital, Nanjing First Hospital,
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35 553 Pingdingshan First People's Hospital, The First Affiliated Hospital of Zhengzhou University,
36
37 554 The Second Hospital of Shanxi Medical University, Xiangya Hospital Central South
38
39 555 University, Wuxi Second People's Hospital, Chenzhou No.1 People's Hospital, Shengjing
40
41 556 Hospital of China Medical University, Yancheng City No.1 People's Hospital, The First
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43 557 People's Hospital of Kunshan, Zhenjiang First People's Hospital.
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55 558 **Disclosure and conflicts of interest**

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559 This work was sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China.

560 All authors declare no conflicts of interest.

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562 **Figure 1. Study flow chart**

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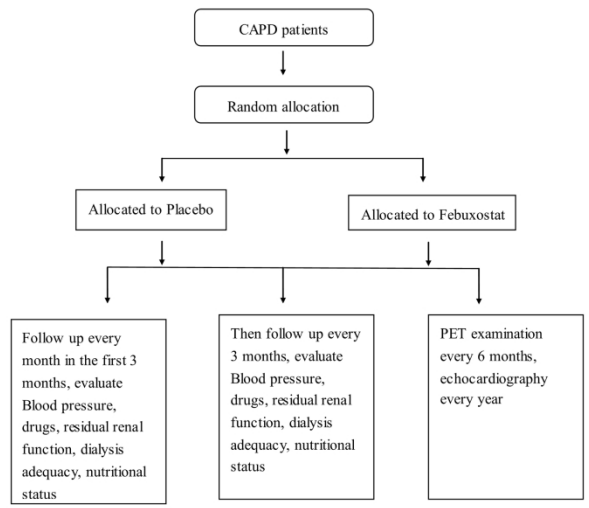
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Figure 1. Study flow chart



Study flow chart

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1 line 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3 line 52-page 4 line 56)
	2b	All items from the World Health Organization Trial Registration Data Set (Not applicable)
Protocol version	3	Date and version identifier (Page 4 line 69-70)
Funding	4	Sources and types of financial, material, and other support (Page 4 line 71 – Page 5 line 81)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Page 5 line 82-Page 7 line 133)
	5b	Name and contact information for the trial sponsor (Page 7 line 134-136)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 7 line 137 –line 140)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 8 line 141-144)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Page 8 line 145- Page 9 line 164)
	6b	Explanation for choice of comparators (Page 9 line 165-171)

1			
2	Objectives	7	Specific objectives or hypotheses (Page 9 line 172-174)
3			
4	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (Page 9 line 175-176)
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10	Methods: Participants, interventions, and outcomes		
11			
12	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (Page 9 line 177-180)
13			
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16	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (Page 9 line 181 - Page 11 line 216)
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22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 11 line 220 - Page 12 line 234)
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27		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (Page 12 line 235 -Page 13 line 258)
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32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 13 line 259 - line 265)
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37		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 13 line 266 -Page 15 line 298)
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40	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (Page 15 line 299-308)
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48	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Page 15 line 309 - Page 17 line 325)
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54	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 17 line 326-332)
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2 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
3 target sample size (**Page 17 line 333 - 338**)
4

5 **Methods: Assignment of interventions (for controlled trials)**
6

7 Allocation:

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9 Sequence generation 16a Method of generating the allocation sequence (eg, computer-
10 generated random numbers), and list of any factors for stratification.
11 To reduce predictability of a random sequence, details of any planned
12 restriction (eg, blocking) should be provided in a separate document
13 that is unavailable to those who enrol participants or assign
14 interventions (**Page 17 line 339-page 18 line 344**)
15
16

17 Allocation concealment 16b Mechanism of implementing the allocation sequence (eg, central
18 telephone; sequentially numbered, opaque, sealed envelopes),
19 describing any steps to conceal the sequence until interventions are
20 assigned (**Page 18 line 345-351**)
21
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23 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
24 and who will assign participants to interventions (**Page 18 line 352-
25 355**)
26

27 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial
28 participants, care providers, outcome assessors, data analysts), and
29 how (**Page 18 line 356 - 364**)
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32 17b If blinded, circumstances under which unblinding is permissible, and
33 procedure for revealing a participant's allocated intervention during
34 the trial (**Page 19 line 365-376**)
35

36 **Methods: Data collection, management, and analysis**
37

38 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other
39 trial data, including any related processes to promote data quality (eg,
40 duplicate measurements, training of assessors) and a description of
41 study instruments (eg, questionnaires, laboratory tests) along with
42 their reliability and validity, if known. Reference to where data
43 collection forms can be found, if not in the protocol (**Page 19 line 377-
44 Page 20 line 388**)
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47 18b Plans to promote participant retention and complete follow-up,
48 including list of any outcome data to be collected for participants who
49 discontinue or deviate from intervention protocols (**Page 20 line 389-
50 392**)
51
52

53 Data management 19 Plans for data entry, coding, security, and storage, including any
54 related processes to promote data quality (eg, double data entry;
55 range checks for data values). Reference to where details of data
56 management procedures can be found, if not in the protocol (**Page 20
57 line 393-Page 21 line 417**)
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- Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (**Page 21 line 418- 429**)
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) (**Page 21 line 430-431**)
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (**Page 22 line 432-436**)

14 **Methods: Monitoring**

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- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (**Page 22 line 437-442**)
- 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (**Page 22 line 443-444**)
- Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (**Page 22 line 445 - Page 23 line 461**)
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (**Page 23 line 462- Page 24 line 476**)

39 **Ethics and dissemination**

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (**Page 24 line 477-479**)
- Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (**Page 24 line 480**)
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (**Page 24 line 481-487**)
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (**Page 24 line 488-489**)

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2	Confidentiality	27	How personal information about potential and enrolled participants will
3			be collected, shared, and maintained in order to protect confidentiality
4			before, during, and after the trial (Page 24 line 490 - 494)
5			
6	Declaration of	28	Financial and other competing interests for principal investigators for
7	interests		the overall trial and each study site (Page 24 line 495-497)
8			
9	Access to data	29	Statement of who will have access to the final trial dataset, and
10			disclosure of contractual agreements that limit such access for
11			investigators (Page 25 line 498-500)
12			
13	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
14	post-trial care		compensation to those who suffer harm from trial participation (Page
15			25 line 501-502)
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18	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
19	policy		participants, healthcare professionals, the public, and other relevant
20			groups (eg, via publication, reporting in results databases, or other
21			data sharing arrangements), including any publication restrictions
22			(Page 25 line 503-505)
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25		31b	Authorship eligibility guidelines and any intended use of professional
26			writers (Page 25 line 505-507)
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28		31c	Plans, if any, for granting public access to the full protocol, participant-
29			level dataset, and statistical code (Page 25 line 505-507)
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32	Appendices		
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34	Informed consent	32	Model consent form and other related documentation given to
35	materials		participants and authorised surrogates (See supplement material
36			Inform consent)
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39	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
40	specimens		specimens for genetic or molecular analysis in the current trial and for
41			future use in ancillary studies, if applicable (Not applicable)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.