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Multicentre, randomised, open-label, phase IV-III study to evaluate the efficacy of cloxacillin plus fosfomicin versus cloxacillin alone in adult patients with methicillin-susceptible *Staphylococcus aureus* bacteraemia: study protocol for the SAFO trial.

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6 **2 efficacy of cloxacillin plus fosfomicin versus cloxacillin alone in adult**
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9 **3 patients with methicillin-susceptible *Staphylococcus aureus***
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12 **4 bacteraemia: study protocol for the SAFO trial.**

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1
2
3 **70 Abstract**
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5
6 **71 Introduction:**
7

8 Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia is a frequent condition,
9
10 with high mortality rates. There is a growing interest in identifying new therapeutic regimens
11
12 able to reduce therapeutic failure and mortality observed with the standard of care of beta-
13
14 lactam monotherapy. *In vitro* and small-scale studies have found synergy between cloxacillin
15
16 and fosfomycin against *S. aureus*. Our aim is to test the hypothesis that cloxacillin plus
17
18 fosfomycin achieves higher treatment success than cloxacillin alone in patients with MSSA
19
20 bacteraemia.
21
22

23
24 **79 Methods:**
25

26 We will perform a superiority, randomised, open-label, phase IV-III, two-armed parallel group
27
28 (1:1) clinical trial at 20 Spanish tertiary hospitals. The trial will be conducted in accordance with
29
30 Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines. Adults
31
32 (≥ 18 years) with isolation of MSSA from at least one blood culture ≤ 72 hours before inclusion
33
34 with evidence of infection, will be randomly allocated to receive either cloxacillin 2g/4h
35
36 intravenous (IV) plus fosfomycin 3 g/6h IV or cloxacillin 2g/4h IV alone for seven days. After the
37
38 first week, sequential treatment and total duration of antibiotic therapy will be determined
39
40 according to clinical criteria by the attending physician.
41
42

43
44 Primary endpoints: 1) Treatment success at day 7, a composite endpoint comprising all the
45
46 following criteria: patient alive, stable or with improved quick-SOFA score, afebrile and with
47
48 negative blood cultures for MSSA at day 7. 2) Treatment success at Test of Cure visit (TOC):
49
50 patient alive and no isolation of MSSA in blood culture or at another sterile site from day 8
51
52 until TOC (12 weeks after randomisation).
53

54
55 We assume a rate of treatment success of 74% in the cloxacillin group. Accepting alpha risk of
56
57 0.05 and beta risk of 0.2 in a two-sided test, 183 subjects will be required in each of the control
58
59
60

95 and experimental groups to obtain statistically significant difference of 12% (considered
96 clinically significant).

97

98 **Ethics and dissemination:** Ethical approval has been obtained from the Ethics Committee of
99 Bellvitge University Hospital (AC069/18) and from the Spanish Medicines and Healthcare
100 Product Regulatory Agency (AEMPS, AC069/18), and is valid for all participating centres under
101 existing Spanish legislation. The results will be presented at international meetings and will be
102 made available to patients and funders.

103 The protocol has been approved by AEMPS with the Trial Registration Number EudraCT 2018-
104 001207-37. ClinicalTrials.gov Identifier: NCT03959345.

105

106 **Strengths and limitations of this study**

107 - This strategic trial is intended to offer clinicians the best antibiotic treatment for MSSA
108 bacteraemia and to determine whether combining cloxacillin and fosfomycin might improve
109 outcomes compared with cloxacillin alone.

110 - The primary endpoints are strong composite outcomes that will assess mortality, clinical and
111 microbiological failure at 7 and 90 days after randomisation.

112 - The multicentre nature of the study supports the generalisability of the results.

113 - The major limitation will be the open-label design. Nevertheless, the participation of a
114 blinded adjudication committee, which will evaluate the key study endpoints, will mitigate the
115 observer bias inherent in the open-label design.

116 - Given the increased risk of sodium overload, patients with cardiac failure and hepatic
117 cirrhosis will be excluded.

118 Introduction

119 *Staphylococcus aureus* is one of the most common causes of bacteraemia and endocarditis in
120 industrialised countries, and has particularly high hospitalisation and mortality rates (and
121 associated costs) [1,2]. Healthcare exposure and the increasing use of invasive devices have
122 contributed to the high burden of the disease [3].

123 Mortality rates due to methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia
124 range between 20 and 30%. Mortality has been linked to factors such as age, co-morbidities,
125 source of infection, pathogen virulence elements and optimisation of antibiotic treatment [4].
126 Complicated *S. aureus* bacteraemia, defined as the persistence of positive blood cultures
127 during the first week of treatment or haematogenous seeding, is common, and is an indicator
128 of poor prognosis [5]. Indeed, every continued day of bacteraemia has been associated with a
129 higher risk of mortality [6,7].

130 Even though MSSA bacteraemia is a common and life-threatening infection, the optimum
131 treatment and its duration has not been well established. Nor is it clear whether monotherapy
132 is better than combination therapy. For over 50 years, the standard treatment of MSSA
133 bacteraemia has been cloxacillin monotherapy [8]. Today, there is a growing interest in
134 identifying new therapeutic regimens able to reduce the rate of therapeutic failure and
135 improve the outcomes obtained with the standard of care.

136 Strategies combining cloxacillin with aminoglycosides have not shown any significant
137 improvement in patients' outcomes, and have been associated with a higher risk of
138 nephrotoxicity [9]. A randomised multicentre study conducted in the UK, which included
139 around 1000 patients and compared the efficacy of the rifampicin combination with the
140 standard treatment for *S. aureus* bacteraemia, did not show a reduction in early or late
141 mortality for the combined therapy compared with monotherapy [10]. Nor did two recent
142 studies comparing a beta-lactam and daptomycin combination with beta-lactams in

1
2
3 143 monotherapy to treat MSSA bacteraemia show any differences in mortality between groups
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5 144 [11, 12].

6
7 145 Among the combinations that might improve the outcome of patients with MSSA bacteraemia,
8
9 146 cloxacillin plus fosfomycin is an appealing strategy. Fosfomycin is a bactericidal antibiotic
10
11 147 which inhibits synthesis of N-acetylmuramic acid, a precursor of bacterial wall peptidoglycan,
12
13 148 and is highly active against most strains of *S. aureus* [13]. Cross-resistance with other antibiotic
14
15 149 groups is very uncommon. Nevertheless, because of the risk of the development of resistance
16
17 150 when administered as monotherapy, fosfomycin must be administered in combination with
18
19 151 another antibiotic. *In vitro* and small scale studies have demonstrated a synergistic effect of
20
21 152 cloxacillin plus fosfomycin against *S. aureus*, and several different beta-lactam combinations
22
23 153 have been successfully used in difficult-to-treat *S. aureus* infections [14, 15, 16].

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25
26
27 154 In a recent multicentre trial, we showed that daptomycin plus fosfomycin in methicillin-
28
29 155 resistant *S.aureus* (MRSA) bacteraemia achieved better outcomes in younger severely ill
30
31 156 patients and faster clearance of bacteraemia than daptomycin alone [17]. To date, however,
32
33 157 no randomised studies evaluating the efficacy of cloxacillin plus fosfomycin for treating MSSA
34
35 158 bacteraemia have been published or registered in the Clinical Trials database.

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38
39 159 **Objective:** To test the hypothesis that combining cloxacillin plus fosfomycin during the initial
40
41 160 seven days of treatment achieves better outcomes than cloxacillin alone in patients with MSSA
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43 161 bacteraemia.

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164 **Methods and analysis**

165 **Study design and setting**

166 We will perform a multicentre, superiority, randomised, open-label, phase IV-III, two-armed
167 parallel group (1:1) clinical trial. Patients will be recruited from 20 tertiary hospitals in Spain (a
168 list of study sites is available in the Supplementary material). The trial has been registered in
169 the EudraCT and ClinicalTrials databases. The protocol follows the Standard Protocol Items:
170 Recommendations for Interventional Trials (SPIRIT) initiatives, and the results will be
171 presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT)
172 statement[18] [19].

173

174 **Study population**

175 *Inclusion criteria:*

- 176 - Subjects aged ≥ 18 years;
- 177 - At least one blood culture positive for MSSA ≤ 72 hours before inclusion, with evidence of
178 active infection;
- 179 - Written informed consent from the participant or the legal representative.

180

181 *Exclusion criteria:*

- 182 - Severe clinical status with expected death < 24 h.
- 183 - Severe hepatic cirrhosis (Child-Pugh C).
- 184 - Moderate-severe cardiac chronic failure (NYHA III-IV).
- 185 - Prosthetic endocarditis.
- 186 - History of significant allergy to β -lactams or fosfomycin (defined as previous type 1
187 hypersensitivity reaction to any β -lactams or fosfomycin, or history of serious non-type 1
188 hypersensitivity reaction to any penicillin or fosfomycin).
- 189 - Known *S. aureus* fosfomycin non-susceptibility.

- 1
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3 190 - Polymicrobial bacteraemia with more than one microorganism in blood cultures.
4
5 191 - A positive pregnancy test or pregnancy or lactation at the time of inclusion.
6
7 192 - Myasthenia gravis.
8
9 193 - Participation in another clinical trial.
10
11
12 194 - Previous participation in the present clinical trial.
13
14 195 - Social problems, cognitive or psychiatric impairment which might be expected to affect
15
16 196 adherence to the protocol.
17
18 197 - Acute SARS-CoV2 infection.
19
20
21 198

199 **Intervention**

200 Patients will be randomly assigned to receive intravenous cloxacillin 2g every four hours plus
201 fosfomycin 3 g every six hours, or to receive cloxacillin 2 g every four hours intravenously for
202 the duration of seven days. If creatinine clearance is <30 mL/min, cloxacillin will be
203 administered at dose of 2g every six hours. The fosfomycin dose will be adjusted according to
204 creatinine clearance, as explained in Table 1.

205 This treatment will be administered during the first seven days after randomisation. After the
206 first week, the choice of antibiotic strategy and the duration of overall antibiotic treatment will
207 be determined according to clinical criteria by the attending physician, based on current
208 guidelines. Uncomplicated bacteraemia will be treated for 10-14 days, and complicated
209 bacteraemia for 4-6 weeks at least, depending on the source of the infection and other clinical
210 considerations. Removal of a focus of infection as soon as possible and performance of
211 echocardiogram will be prioritised. The assessment schedule is summarised in Table 2. A
212 schematic diagram of study design is shown in Figure 1.

213

214 **Outcomes**

1
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3 215 Efficacy will be analysed by intention to treat in all randomised patients, using a hierarchical
4
5 216 testing procedure in the following order: treatment success at day 7 followed by treatment
6
7 217 success at TOC visit.
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11
12 219 **Primary endpoints:**

13
14 220 Treatment success at day 7 is a composite outcome defined by all the following criteria met
15
16 221 after randomisation:

- 17
18 222 - Patient alive at day 7 AND
19
20 223 - Clinical improvement measured by stable or improved quick SOFA score (compared
21
22 224 with baseline) at day 7 AND
23
24 225 - Patient afebrile at day 7 AND
25
26 226 - Negative MSSA blood cultures at day 7.

27
28 227 Treatment success at TOC visit, defined by presence of all of the following:

- 29
30 228 - Patient alive at TOC;
31
32 229 - No isolation of MSSA in blood culture or at another sterile site from day 8 until the
33
34 230 TOC visit (12 weeks after randomisation). In case of patients with a prolonged course
35
36 231 of antibiotic treatment (more than 10 weeks), the TOC visit will be performed two
37
38 232 weeks after the end of treatment (EOT).
39
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43 233

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45 234 Treatment failure is defined by the presence of one of the following conditions: all-cause
46
47 235 mortality at TOC, withdrawal from the study due to adverse events related to the treatment,
48
49 236 requirement of an additional MSSA-active antibiotic until day 7, and lack of clinical
50
51 237 improvement at day 7.
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55
56 239 **Secondary endpoints**

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58 240 *Clinical:*
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3 241 - All-cause mortality at day 7, EOT and TOC visit.
4
5 242 - Persistent bacteraemia (at least one positive blood culture) at day 3 and persistent
6
7 243 bacteraemia at day 7 after randomisation.
8
9
10 244 - Microbiological relapse, defined by at least one positive blood culture for MSSA at
11
12 245 least 72 hours after a preceding negative culture.
13
14 246 - Microbiological treatment failure, defined by a positive sterile site culture for MSSA at
15
16 247 least 14 days after randomisation.
17
18 248 - Number of patients with persistent and relapsing bacteraemia.
19
20
21 249 - Number of patients with complicated bacteraemia, defined as persistent bacteraemia,
22
23 250 endocarditis or metastatic emboli, presence of prosthetic devices.
24
25 251 - Length of intensive care unit stay.
26
27
28 252 - Duration of intravenous antibiotic treatment.
29
30 253 We will perform exploratory subgroup analyses for patients at high risk (those with persistent
31
32 254 bacteraemia, metastatic infection, unknown focus of bacteraemia, endocarditis, and
33
34 255 pneumonia).
35
36
37 256
38
39 257 *Microbiological:*
40
41 258 - *In vitro* cloxacillin plus fosfomycin combination synergy.
42
43 259 - Emergence of fosfomycin-resistant strains during therapy in the combination
44
45 260 treatment arm.
46
47
48 261 - Operon *agr* functionality and its relationship with Minimum Inhibitory Concentration
49
50 262 (MIC) changes to vancomycin (VAN) and daptomycin (DAP) and with biofilm
51
52 263 production.
53
54 264 - VAN and DAP MIC as markers of complications during bacteraemia.
55
56
57 265 - Whole genome sequencing and its changes in patients with treatment failure.
58
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3 267 *Pharmacological:*
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5 268 Patients recruited at the coordinating centre (Bellvitge University Hospital) will be included in a
6
7 269 pharmacological sub-study, after obtaining additional signed informed consent. The variables
8
9 270 assessed will be:

11 271 - Minimum and maximum concentration in steady state of fosfomycin and cloxacillin,
12
13 272 and pharmacokinetic variability of these concentrations.

14
15
16 273 - Associations between pharmacokinetic parameters and efficacy.
17
18
19 274

20
21 275 *Safety:*
22

23 276 Safety of cloxacillin plus fosfomycin as compared with cloxacillin alone.
24
25 277

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27
28 278 **Follow-up and data collection**

29
30 279 During the first week of treatment, all patients will be assessed at days 1, 3 and 7 by a member
31
32 280 of the investigating team, and followed up daily by an infectious diseases specialist. Scheduled
33
34 281 visits are reported in Table 2. A follow-up visit will be arranged for all participants at EOT (48h
35
36 282 after the last dose of antibiotic treatment) and at TOC. At this last visit, a structured telephone
37
38 283 interview will be performed to assess outcomes.

39
40
41 284 All data will be recorded on a secure web application used for building and managing online
42
43 285 databases (REDCap). Authorised staff will be free to examine the records for quality assurance
44
45 286 and audit purposes.
46
47 287

48
49
50 288 **Endpoint assessment**

51
52
53 289 The primary endpoints will be assessed by a committee comprising three independent senior
54
55 290 infectious disease specialists with extensive experience in *S. aureus* bacteraemia and
56
57 291 endocarditis. This committee will be blinded to treatment allocation and to patient
58
59 292 identification. Committee members will receive a data extract containing patients'

1
2
3 293 demographical data, comorbidities, source of infection, quick SOFA score at baseline and day
4
5 294 7, date and results of blood and sterile cultures between randomisation and TOC, as well as
6
7 295 date of death if applicable.
8

9
10 296

11 297 **Statistical analysis plan**

12 298 *Sample size*

13
14
15
16 299 Prior data indicate a success rate in the cloxacillin alone group of 74% [11]. To achieve a
17
18 300 success rate in the experimental group of 86% (i.e., an absolute difference of 12%, considered
19
20 301 as clinically significant) we will need 183 experimental subjects and 183 control subjects to
21
22 302 reject the null hypothesis of an equal success rate with a probability of 80%. The probability of
23
24 303 type I error associated with this test is 5%, and a drop-out rate of 5% has been anticipated.
25
26

27 304 *Allocation*

28
29 305 Participants will be block randomised to receive monotherapy or combination using an
30
31 306 internet-based, concealed computer-generated random allocation sequence. Random blocks
32
33 307 will be of size 4 or 6. The randomised sequence allocation will be stored in the Biostatistics
34
35 308 Unit at Biomedical Research Institute of Bellvitge (IDIBELL) and will not be available to any
36
37 309 member of the research team.
38
39

40 310 *Data analysis*

41
42 311 The main analysis will be performed for the intention to treat population, which will include all
43
44 312 randomised patients included in the study with a primary outcome assessment. If no statistical
45
46 313 significance is detected by day 7 in the hierarchy, then no further hypothesis testing will be
47
48 314 performed. The analysis will be repeated in the per protocol population. All patients who
49
50 315 receive at least one dose of treatment will be included in the safety analysis.
51
52

53
54 316 The Chi-square test will be used to test the binary endpoints of the success rate. The relative
55
56 317 risk for success rate will be calculated, accompanied by 95% confidence intervals. The time-to-
57
58 318 event outcomes, including the time of response, and overall survival will be estimated using
59
60

1
2
3 319 the Kaplan-Meier method [20]. All analyses and data management will be performed with R
4
5 320 software, version 4.0.4 or superior [21].
6
7
8 321

9
10 322 **Monitoring**

11
12 323 *Monitoring plans*

13
14 324 The data monitoring board will ensure the correct progress of the study in terms of safety, and
15
16 325 also the sample size assumptions.

17
18 326 *Harms - Data Safety and Monitoring Board (DSMB)*

19
20 327 An independent DSMB will review safety data and provide advice about the continuation,
21
22 328 modification and/or termination of the study, as well as adherence to the protocol,
23
24 329 recruitment, outcomes and additional data related to participants' safety. The DSMB will be
25
26 330 composed by specialists in pharmacology, biostatistics and infectious diseases. The review by
27
28 331 the DSMB will be performed when half of the sample size will be reached.

29
30 332 *Adverse events reporting and quantification*

31
32 333 An adverse event will be defined as any injury related to medical management occurring
33
34 334 during the patient's participation in the study, even if it is not related to the study medication.

35
36 335 An adverse drug event will be defined as any medication-related adverse event occurring
37
38 336 during the patient's participation in the clinical trial.

39
40 337 An adverse drug reaction will be defined as any 'adverse drug event' occurring when the
41
42 338 medication is used as directed and at the usual dosage.

43
44 339 Serious adverse event or reaction will be defined as an event or reaction that:

- 45
46 340 - Results in death;
47
48 341 - Is life-threatening;
49
50 342 - Causes persistent or significant disability;
51
52 343 - Causes a congenital anomaly/birth defect;
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3 344 - Requires in-patient hospitalisation or prolongation of existing hospitalisation (not
4
5 345 related to basal diseases).
6

7 346 *Adverse drug events of particular interest for the study*

- 9
10 347 - Hypokalaemia and hypocalcaemia: blood analysis will be performed every 2-3 days
11
12 348 during the first week to permit potassium and calcium control. Furthermore,
13
14 349 administration of potassium supplement will be recommended from the first day of
15
16 350 treatment to avoid this complication.
17
18 351 - Sodium overload: since both fosfomycin and cloxacillin carry a high sodium load, daily
19
20 352 physical examination and administration of a low dose of a diuretic such as furosemide
21
22 353 will be recommended to avoid hypertension, oedema and acute cardiac failure.
23
24

25 354 *Reporting*

26
27 355 Any adverse events occurring during the patient's participation in the clinical trial will be
28
29 356 recorded on the clinical chart by the principal investigator at each scheduled visit. The principal
30
31 357 investigator will record its possible relationship to the study drug.
32
33

34 358 The electronic case report form should record only the following: serious adverse drug events;
35
36 359 adverse events (of any degree) related to the study medication, in the opinion of the PI;
37
38 360 adverse events (of any degree) leading to modification of the dosage of the study drug or its
39
40 361 interruption/early discontinuation; adverse events of particular interest for the study.
41
42

43 362 The sponsor will be notified of all serious adverse events within 24 h of their occurrence.
44
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48 364 **Trial status**

49
50 365 The SAFO trial opened its first recruitment site on 31 May 2019. The first patient was enrolled
51
52 366 on 1 July 2019. Follow up is expected to be completed by May 2022.
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55
56 368 **Declaration**

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59 369 *Ethics*
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3 370 The trial will be conducted in accordance with the principles of the most recent Declaration of
4
5 371 Helsinki (agreed by the 64th World Medical Association General Assembly in 2013), the Good
6
7 372 Clinical Practice (GCP) guidelines, and the current legislation. The investigator is responsible for
8
9
10 373 guaranteeing that the clinical trial is conducted in compliance with the directives established
11
12 374 by the International Conference on Harmonisation GCP guidelines and with local legislation.
13
14 375 The study was authorised by the Spanish Medicines and Healthcare Products Regulatory
15
16 376 Agency (AEMPS, 18-0905) and by the Bellvitge University Hospital Ethics committee
17
18 377 (AC069/18).
19
20
21 378 The principal investigator or collaborator at each site will provide patients with the information
22
23 379 sheet, and s/he will explain the nature of the study and the objectives and clarify any doubts.
24
25 380 Written informed consent will be obtained from all patients or from their legal representatives
26
27 381 (LRs) if they lack capacity, before enrolment. Patients (or their LRs) are free to withdraw from
28
29 382 the trial at any time; this will be explicitly stated on the patient's information sheet.
30
31
32 383 Patients' personal and clinical information will be managed in accordance with European
33
34 384 Regulation 2016/679 and Spanish legislation. Patients' data will be anonymised; each patient
35
36 385 will be identified by a code. Only the study physician and collaborators will have access to
37
38 386 patients' clinical histories. Consequently, patients' identities will not be revealed to any other
39
40 387 person, except in cases of medical emergency or if required by law. Access to patient
41
42 388 information will be restricted to the study physician and collaborators, the health authorities
43
44 389 (AEMPS), the Clinical Research Ethics Committee, and personnel authorised by the sponsor
45
46 390 when they need to check the data and procedures used in the study, but always maintaining
47
48 391 the confidentiality of the information in accordance with the current legislation. The trial
49
50 392 protocol was approved by the research ethics committee on 28 March 2019 and by the AEMPS
51
52 393 on 8 April 2019. The informed consent form and information sheet were approved by the
53
54 394 research ethics committee on 28 March 2019. The emendation was approved by the research
55
56 395 ethics committee and by the AEMPS on 29 November 2019.
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3 396 *Data sharing plan and dissemination*
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5 397 Sharing of data generated by this project is an essential part of our proposed activities and will
6
7 398 be carried out in several different ways. We would wish to make our results available both to
8
9 399 the community of scientists interested in infectious diseases and the biology of *Staphylococcus*
10
11 400 *aureus* to avoid unintentional duplication of research.
12
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14 401 The preliminary results will be presented at international and national infectious diseases
15
16 402 conferences and will be published in peer-reviewed journals. The results will also be made
17
18 403 available to patients, caregivers and funders through press and social media communications.
19

20
21 404 A corporative *Twitter* account will be created to establish direct contact with the general
22
23 405 public and other health-care professionals. Any formal presentation or publication of data
24
25 406 collected from this study will be considered as a joint publication by the participating
26
27 407 investigators and will follow the recommendations of the International Committee of Medical
28
29 408 Journal Editors (ICMJE).
30

31
32 409 Individual participant data that underlie the results, after deidentification (text, tables, figures,
33
34 410 and appendices) will be available immediately following publication and ending 5 years
35
36 411 following article publication. Data will be shared with researchers who provide a
37
38 412 methodologically sound proposal to achieve aims in the approved suggestions. Propositions
39
40 413 should be directed to the corresponding author.
41
42

43 414 *Patients and public involvement*
44

45 415 Patients will not be involved in either the enrolment or the execution of the trial, or in the
46
47 416 assessment of the interventions. However, before the beginning of the study, a number of
48
49 417 patients with previous *S. aureus* bacteraemia were contacted by phone to obtain their
50
51 418 feedback about the study.
52
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56 420 **Protocol amendments**
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3 421 No protocol modifications will become effective until approved by the relevant authorities and
4
5 422 by the Drug Research Ethics Committee (CEIm). Exceptions will be made for any changes to
6
7 423 protect patients from imminent harm and those concerning exclusively logistic or
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9 424 administrative aspects.
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3 489 *Authors' contributions*
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6 490 SG, GC, JC and MP conceived and designed the study. SG, GC and MP wrote and revised the
7
8 491 manuscript. PH and SB critically reviewed the protocol. All authors have read and approved the
9
10 492 final manuscript.
11
12

13 493 *Trial sponsor:* Miquel Pujol, MD PhD. Department of Infectious Diseases, Hospital Universitari
14
15 494 de Bellvitge, Institut Investigacions Biomèdiques de Bellvitge (IDIBELL), Carrer de la Feixa
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17 495 Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona. Tel.: +34. 93 2602487
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23

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25
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27
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30
31 500 2021 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de
32
33 501 Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish
34
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36
37

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39
40

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42
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44
45 506 for technical help.
46
47
48

49 507 *Competing interests*
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51

52 508 GH received a research grant from ERN (19PNJ145).
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55 509 *List of abbreviation*
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- 510 MSSA: Methicillin-susceptible *Staphylococcus aureus* bacteraemia. TOC: test of cure. SPIRIT:
- 511 Standard Protocol Items: Recommendation for Interventional Trials. CONSORT: Consolidated
- 512 Standards of Reporting Trials. SOFA: Sequential Organ Failure Assessment. MRSA: Methicillin-
- 513 resistant *Staphylococcus aureus*. EOT: End of Treatment. GCP: Good Clinical Practice.

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514 **Tables**515 **Table 1.** Fosfomycin dosage adjusted to renal function.

Creatinine clearance (mL/min)	Fosfomycin dosage
>40	3 g every 6 hours
20-40	3 g every 12 hours
10-20	3g every 24 hours
<10	3 g every 48 hours
Haemodialysis	3 g after haemodialysis
Continuous renal replacement therapy	3 g every 24 hours

516 Abbreviations: mL: millilitre; min: minute.

517 **Table 2.** The SAFO evaluation schedule.

	Visit				Unscheduled			
	Day	Screening	0	3	7	EOT	Visit ¹	TOC
All patients								
Eligibility criteria		X						
Pregnancy test ²		X						
Informed consent		X						
Randomisation			X					
Clinical evaluation			X	X	X	X	X	X ³
Quick SOFA score			X		X			
Blood cultures			X	X	X	X	X	X ³
Blood count and biochemical analysis ⁴			X	X	X		X	X ³
Adverse events record				X	X	X	X	X
Concomitant medication			X	X	X	X		
Subgroup of patients with PK/PD sub analysis								
Lithium heparin blood sample (2x 5mL)					X			

518 ¹Unscheduled visit will be performed only in case of clinical infectious symptoms and signs.519 ²Pregnancy test will be performed only in woman of childbearing age.520 ³In absence of infective symptoms, clinical assessment may be made by phone call; blood culture and
521 blood analysis will not be necessary.522 ⁴Complete blood count, biochemical analysis (C-reactive protein-, creatinine, urea, creatinine clearance,
523 AST, ALT, bilirubin, sodium, potassium, calcium, acid-base analysis) and coagulation test (prothrombin
524 test/INR).

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3 525 **Figures**
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6 526 **Figure 1.** Study design.
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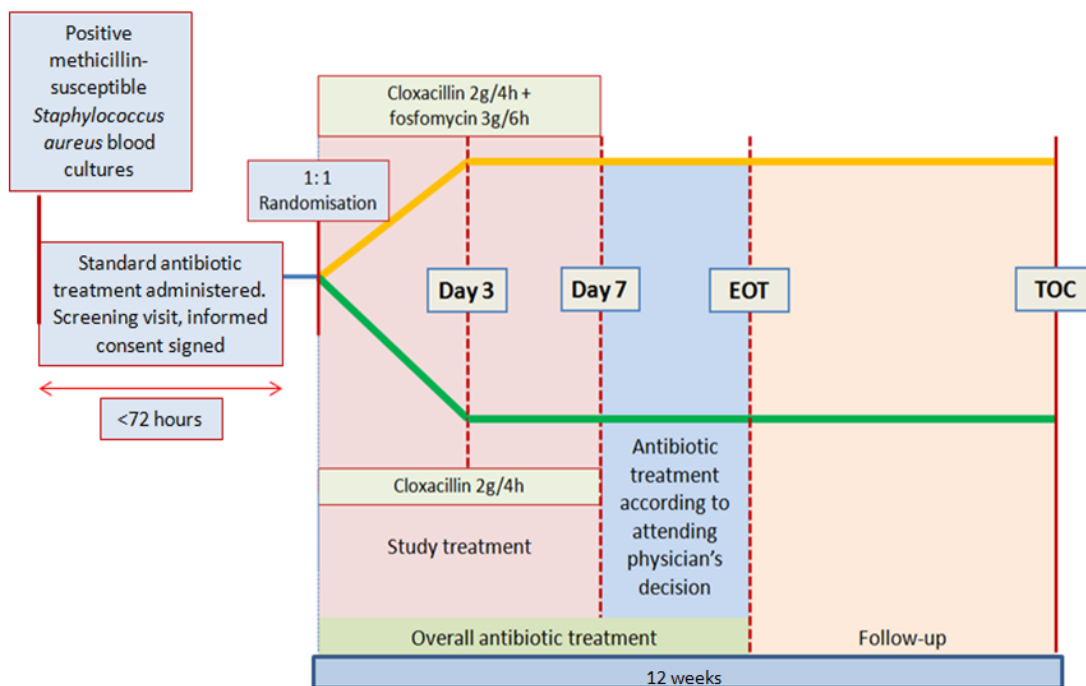
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3 530 **Supplementary material**
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- 6 531 **List of study sites:** Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona;
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8 532 Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona;
9
10 533 Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona;
11
12 534 Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mútua de Terrassa,
13
14 535 Barcelona; Corporació Sanitaria Parc Taulí, Sabadell, Barcelona; Hospital Universitari Sant Joan,
15
16 536 Reus; Hospital Universitario M.Broggi, Sant Joan Despí, Barcelona; Hospital Universitario 12 de
17
18 537 Octubre, Madrid; Hospital Universitario Virgen Macarena, Seville; Hospital Universitario de
19
20 538 Cruces, Barakaldo; Hospital Universitario Lucus Augusti, Lugo; Hospital Clínico Universitario de
21
22 539 Zaragoza, Zaragoza; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitari
23
24 540 Germans Trias, Badalona; Hospital Universitario Álvaro Cunqueiro, Vigo; Hospital de Barcelona,
25
26 541 Barcelona; Hospital Universitario La Paz, Madrid.
27
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30 542 Other hospitals may be added during the course of the clinical trial.
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Supplementary material

List of study sites: Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona; Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona; Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona; Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mútua de Terrassa, Barcelona; Corporació Sanitaria Parc Taulí, Sabadell, Barcelona; Hospital Universitari Sant Joan, Reus; Hospital Universitario M.Broggi, Sant Joan Despí, Barcelona; Hospital Universitario 12 de Octubre, Madrid; Hospital Universitario Virgen Macarena, Seville; Hospital Universitario de Cruces, Barakaldo; Hospital Universitario Lucus Augusti, Lugo; Hospital Clínico Universitario de Zaragoza, Zaragoza; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitari Germans Trias, Badalona; Hospital Universitario Álvaro Cunqueiro, Vigo; Hospital de Barcelona, Barcelona; Hospital Universitario La Paz, Madrid.

Other hospitals may be added during the course of the clinical trial.



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

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	21
	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	12
	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)	12
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	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
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)	8

Methods: Participants, interventions, and outcomes

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	8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	10
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)	23
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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	13
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	13
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	12
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13				
14				
15		17b	If blinded, circumstances under which unblinding is permissible, and	NA
16			procedure for revealing a participant's allocated intervention during	
17			the trial	
18				
19				

Methods: Data collection, management, and analysis

20				
21				
22	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	12
23	methods		trial data, including any related processes to promote data quality (eg,	
24			duplicate measurements, training of assessors) and a description of	
25			study instruments (eg, questionnaires, laboratory tests) along with	
26			their reliability and validity, if known. Reference to where data	
27			collection forms can be found, if not in the protocol	
28				
29				
30		18b	Plans to promote participant retention and complete follow-up,	
31			including list of any outcome data to be collected for participants who	
32			discontinue or deviate from intervention protocols	
33				
34	Data	19	Plans for data entry, coding, security, and storage, including any	12
35	management		related processes to promote data quality (eg, double data entry;	
36			range checks for data values). Reference to where details of data	
37			management procedures can be found, if not in the protocol	
38				
39				
40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	13
41	methods		Reference to where other details of the statistical analysis plan can be	
42			found, if not in the protocol	
43				
44				
45		20b	Methods for any additional analyses (eg, subgroup and adjusted	12
46			analyses)	
47				
48		20c	Definition of analysis population relating to protocol non-adherence	13
49			(eg, as randomised analysis), and any statistical methods to handle	
50			missing data (eg, multiple imputation)	
51				

Methods: Monitoring

52				
53				
54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	14
55			and reporting structure; statement of whether it is independent from	
56			the sponsor and competing interests; and reference to where further	
57			details about its charter can be found, if not in the protocol.	
58			Alternatively, an explanation of why a DMC is not needed	
59				
60				

1				
2		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	14
3				
4				
5				
6	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	14
7				
8				
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
12				
13				
14				
15				
16	Ethics and dissemination			
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
18				
19				
20	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)	17
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
27				
28				
29				
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
31				
32				
33	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
41				
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45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
49				
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54		31b	Authorship eligibility guidelines and any intended use of professional writers	
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57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if 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](#)" license.

For peer review only

BMJ Open

Multicentre, randomised, open-label, phase IV-III study to evaluate the efficacy of cloxacillin plus fosfomicin versus cloxacillin alone in adult patients with methicillin-susceptible *Staphylococcus aureus* bacteraemia: study protocol for the SAFO trial.

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6 **2 efficacy of cloxacillin plus fosfomycin versus cloxacillin alone in adult**
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9 **3 patients with methicillin-susceptible *Staphylococcus aureus***
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12 **4 bacteraemia: study protocol for the SAFO trial.**

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30 68

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1
2
3 **70 Abstract**
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5
6 **71 Introduction:**
7

8 Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia is a frequent condition,
9
10 with high mortality rates. There is a growing interest in identifying new therapeutic regimens
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12 able to reduce therapeutic failure and mortality observed with the standard of care of beta-
13
14 lactam monotherapy. *In vitro* and small-scale studies have found synergy between cloxacillin
15
16 and fosfomycin against *S. aureus*. Our aim is to test the hypothesis that cloxacillin plus
17
18 fosfomycin achieves higher treatment success than cloxacillin alone in patients with MSSA
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20 bacteraemia.
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23
24 **79 Methods:**
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26 We will perform a superiority, randomised, open-label, phase IV-III, two-armed parallel group
27
28 (1:1) clinical trial at 20 Spanish tertiary hospitals. The trial will be conducted in accordance with
29
30 Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines. Adults
31
32 (≥ 18 years) with isolation of MSSA from at least one blood culture ≤ 72 hours before inclusion
33
34 with evidence of infection, will be randomly allocated to receive either cloxacillin 2g/4h
35
36 intravenous (IV) plus fosfomycin 3 g/6h IV or cloxacillin 2g/4h IV alone for seven days. After the
37
38 first week, sequential treatment and total duration of antibiotic therapy will be determined
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40 according to clinical criteria by the attending physician.
41
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43
44 Primary endpoints: 1) Treatment success at day 7, a composite endpoint comprising all the
45
46 following criteria: patient alive, stable or with improved quick-SOFA score, afebrile and with
47
48 negative blood cultures for MSSA at day 7. 2) Treatment success at Test of Cure visit (TOC):
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50 patient alive and no isolation of MSSA in blood culture or at another sterile site from day 8
51
52 until TOC (12 weeks after randomisation).
53

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55 We assume a rate of treatment success of 74% in the cloxacillin group. Accepting alpha risk of
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57 0.05 and beta risk of 0.2 in a two-sided test, 183 subjects will be required in each of the control
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3 95 and experimental groups to obtain statistically significant difference of 12% (considered
4
5 96 clinically significant).

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7 97

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9
10 98 **Ethics and dissemination:** Ethical approval has been obtained from the Ethics Committee of
11
12 99 Bellvitge University Hospital (AC069/18) and from the Spanish Medicines and Healthcare
13
14 100 Product Regulatory Agency (AEMPS, AC069/18), and is valid for all participating centres under
15
16 101 existing Spanish legislation. The results will be presented at international meetings and will be
17
18 102 made available to patients and funders.

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20
21 103 The protocol has been approved by AEMPS with the Trial Registration Number EudraCT 2018-
22
23 104 001207-37. ClinicalTrials.gov Identifier: NCT03959345.

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27
28 106 **Strengths and limitations of this study**

29
30 107 - This strategic trial is intended to determine whether combining cloxacillin and fosfomycin
31
32 108 might improve outcomes compared with cloxacillin alone.

33
34 109 - The primary endpoints are strong composite outcomes that will assess mortality, clinical and
35
36 110 microbiological failure at 7 and 90 days after randomisation.

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41 112 -A blinded adjudication committee will evaluate the key study endpoints and mitigate the
42
43 113 observer bias inherent in the open-label design.

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45 114 - Given the increased risk of sodium overload, patients with cardiac failure and hepatic
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47 115 cirrhosis will be excluded.

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116 Introduction

117 *Staphylococcus aureus* is one of the most common causes of bacteraemia and endocarditis in
118 industrialised countries, and has particularly high hospitalisation and mortality rates (and
119 associated costs) [1,2]. Healthcare exposure and the increasing use of invasive devices have
120 contributed to the high burden of the disease [3].

121 Mortality rates at 90 days due to methicillin-susceptible *Staphylococcus aureus* (MSSA)
122 bacteraemia range between 20 and 30% [4][5]. Mortality has been linked to factors such as
123 age, co-morbidities, source of infection, pathogen virulence elements and optimisation of
124 antibiotic treatment [6]. Complicated *S. aureus* bacteraemia is common, and is an indicator of
125 poor prognosis [7]. Indeed, every continued day of bacteraemia has been associated with a
126 higher risk of mortality [8][9].

127 Even though MSSA bacteraemia is a common and life-threatening infection, up to date, it is
128 not clear whether combination therapy could reduce duration of bacteremia or reduce
129 mortality compared with the current standard of care (monotherapy beta-lactams). For over
130 50 years, the standard treatment of MSSA bacteraemia has been antistaphylococcal penicillin
131 monotherapy [10]. Today, there is a growing interest in identifying new therapeutic regimens
132 able to reduce the rate of therapeutic failure and improve the outcomes obtained with the
133 standard of care.

134 Strategies combining cloxacillin with aminoglycosides have not shown any significant
135 improvement in patients' outcomes, and have been associated with a higher risk of
136 nephrotoxicity [11]. A randomised multicentre study conducted in the UK, which included
137 around 1000 patients and compared the efficacy of the rifampicin combination with the
138 standard treatment for *S. aureus* bacteraemia, did not show a reduction in early or late
139 mortality for the combined therapy compared with monotherapy [12]. Nor did two recent
140 studies comparing a beta-lactam and daptomycin combination with beta-lactams in

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2
3 141 monotherapy to treat MSSA bacteraemia show any differences in mortality between groups
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5 142 [13][4].

6
7 143 Among the combinations that might improve the outcome of patients with MSSA bacteraemia,
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9 144 cloxacillin plus fosfomycin is an appealing strategy. Fosfomycin is a bactericidal antibiotic
10
11 145 which inhibits synthesis of N-acetylmuramic acid, a precursor of bacterial wall peptidoglycan,
12
13 146 and is highly active against most strains of *S. aureus* [14]. Cross-resistance with other antibiotic
14
15 147 groups is very uncommon. Nevertheless, because of the risk of the development of resistance
16
17 148 when administered as monotherapy, fosfomycin must be administered in combination with
18
19 149 another antibiotic [15]. *In vitro* and small scale studies have demonstrated a synergistic effect
20
21 150 of cloxacillin plus fosfomycin against *S. aureus* [16], and several different beta-lactam
22
23 151 combinations have been successfully used in difficult-to-treat methicillin-resistant *S. aureus*
24
25 152 (MRSA) infections [17][18].

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30 153 In a recent multicentre trial, we showed that daptomycin plus fosfomycin in MRSA
31
32 154 bacteraemia achieved better outcomes in a subgroup of younger severely ill patients and
33
34 155 faster clearance of bacteraemia than daptomycin alone [19]. To date, however, no other
35
36 156 randomised studies evaluating the efficacy of cloxacillin plus fosfomycin for treating MSSA
37
38 157 bacteraemia have been published or registered in the Clinical Trials database.

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40
41 158 **Objective:** To test the hypothesis that combining cloxacillin plus fosfomycin during the initial
42
43 159 seven days of treatment achieves better outcomes than cloxacillin alone in patients with MSSA
44
45 160 bacteraemia.

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163 **Methods and analysis**

164 **Study design and setting**

165 We will perform a multicentre, superiority, randomised, open-label, phase IV-III, two-armed
166 parallel group (1:1) clinical trial. Patients will be recruited from 20 tertiary hospitals in Spain (a
167 list of study sites is available in the Supplementary material). The trial has been registered in
168 the EudraCT and ClinicalTrials databases. The protocol follows the Standard Protocol Items:
169 Recommendations for Interventional Trials (SPIRIT) initiatives, and the results will be
170 presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT)
171 statement[20] [21].

173 **Study population**

174 *Inclusion criteria:*

- 175 - Subjects aged ≥ 18 years;
- 176 - At least one blood culture positive for MSSA ≤ 72 hours before inclusion, with evidence of
177 active infection;
- 178 - Written informed consent from the participant or the legal representative.

180 *Exclusion criteria:*

- 181 - Severe clinical status with expected death < 24 h.
- 182 - Severe hepatic cirrhosis (Child-Pugh C).
- 183 - Moderate-severe cardiac chronic failure (NYHA III-IV).
- 184 - Prosthetic endocarditis.
- 185 - History of significant allergy to β -lactams or fosfomycin (defined as previous type 1
186 hypersensitivity reaction to any β -lactams or fosfomycin, or history of serious non-type 1
187 hypersensitivity reaction to any penicillin or fosfomycin).
- 188 - Known *S. aureus* fosfomycin non-susceptibility.

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3 189 - Polymicrobial bacteraemia with more than one microorganism in blood cultures.
4
5 190 - A positive pregnancy test or pregnancy or lactation at the time of inclusion.
6
7 191 - Myasthenia gravis.
8
9 192 - Participation in another clinical trial.
10
11 193 - Previous participation in the present clinical trial.
12
13 194 - Social problems, cognitive or psychiatric impairment which might be expected to affect
14 adherence to the protocol.
15
16 195
17
18 196 - Acute SARS-CoV2 infection.
19
20
21 197

198 **Intervention**

199 Patients will be randomly assigned to receive intravenous cloxacillin 2g every four hours plus
200 fosfomycin 3 g every six hours, or to receive cloxacillin 2 g every four hours intravenously for
201 the duration of seven days. If creatinine clearance is <30 mL/min, cloxacillin will be
202 administered at dose of 2g every six hours. The fosfomycin dose will be adjusted according to
203 creatinine clearance, as explained in Table 1.

204 This treatment will be administered during the first seven days after randomisation. After the
205 first week, the choice of antibiotic strategy and the duration of overall antibiotic treatment will
206 be determined according to clinical criteria by the attending physician, based on current
207 guidelines. Uncomplicated bacteraemia (no evidence of complicated bacteraemia) will be
208 treated for 10-14 days, and complicated bacteraemia (defined as infection with hematogenous
209 seeding, progression of infection beyond the primary focus, persistent bacteraemia, skin
210 alterations suggestive of acute systemic infection, presence of noncatheter device,
211 haemodialysis) for 4-6 weeks at least, depending on the source of the infection and other
212 clinical considerations [22][23]. Removal of a focus of infection as soon as possible and
213 performance of echocardiogram will be prioritised. The assessment schedule is summarised in
214 Table 2. A schematic diagram of study design is shown in Figure 1.

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5 216 **Outcomes**

7 217 Efficacy will be analysed by intention to treat in all randomised patients, using a hierarchical
8
9 218 testing procedure in the following order: treatment success at day 7 followed by treatment
10
11
12 219 success at TOC visit. Furthermore, a per-protocol analysis will also be performed.
13

14 220

16 221 **Primary endpoints:**

18 222 Treatment success at day 7 from randomization is a composite outcome defined by all the
19
20
21 223 following criteria met after randomisation:
22

- 23 224 - Patient alive at day 7 AND
24
25 225 - Clinical improvement measured by stable or improved quick SOFA score (compared
26
27 226 with baseline) at day 7 AND
28
29
30 227 - Patient afebrile at day 7 AND
31
32 228 - Negative MSSA blood cultures at day 7.
33

34 229 Treatment success at TOC visit, defined by presence of all of the following:
35

- 36 230 - Patient alive at TOC;
37
38
39 231 - No isolation of MSSA in blood culture and/or at another sterile site from day 8 until
40
41 232 the TOC visit (12 weeks after randomisation). In case of patients with a prolonged
42
43 233 course of antibiotic treatment (more than 10 weeks), the TOC visit will be performed
44
45 234 two weeks after the end of treatment (EOT).
46

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48 235

50 236 Treatment failure is defined by the presence of one of the following conditions: all-cause
51
52 237 mortality at TOC, withdrawal from the study due to adverse events related to the treatment,
53
54 238 requirement of an additional MSSA-active antibiotic until day 7, and lack of clinical
55
56
57 239 improvement at day 7.
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3 241 **Secondary endpoints**
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5 242 *Clinical:*
6

- 7 243 - All-cause mortality at day 7, EOT and TOC visit.
8
9 244 - Persistent bacteraemia (at least one positive blood culture) at day 3 and persistent
10
11
12 245 bacteraemia at day 7 after randomisation.
13
14 246 - Microbiological relapse, defined by at least one positive blood culture for MSSA at
15
16 247 least 72 hours after a preceding negative culture.
17
18 248 - Microbiological treatment failure, defined by a positive sterile site culture for MSSA at
19
20 249 least 14 days after randomisation.
21
22
23 250 - Number of patients with persistent and relapsing bacteraemia.
24
25 251 - Number of patients with complicated bacteraemia, defined as persistent bacteraemia,
26
27 252 endocarditis or metastatic emboli, presence of prosthetic devices.
28
29
30 253 - Length of intensive care unit stay.
31
32 254 - Duration of intravenous antibiotic treatment.
33

34 255 We will perform exploratory subgroup analyses for patients at high risk (those with metastatic
35
36 256 infection, unknown focus of bacteremia, endocarditis, and pneumonia) for both primary
37
38 257 outcomes. On participants with persistent bacteremia subgroup analysis will be focused on
39
40 258 treatment success at TOC.
41
42

43 259

44
45 260 *Microbiological:*
46

- 47 261 - *In vitro* cloxacillin plus fosfomicin combination synergy (see Supplementary material).
48
49 262 - Emergence of fosfomicin-resistant strains during therapy in the combination
50
51 263 treatment arm.
52
53
54 264 - Operon *agr* functionality and its relationship with Minimum Inhibitory Concentration
55
56 265 (MIC) changes to vancomycin (VAN) and daptomycin (DAP) and with biofilm
57
58 266 production.
59
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3 267 - VAN and DAP MIC as markers of complications during bacteraemia. Isolates with rising
4
5 268 vancomycin MICs are associated with thicker cell walls and dysfunctional *agr* profiles,
6
7 269 involved in quorum sensing and activation of *S. aureus* toxins and other virulence
8
9 270 factors, this leads to more resistant but less virulent strains.
10
11
12 271 - Whole genome sequencing and its changes in patients with treatment failure.
13

14 272

15
16 273 *Pharmacological:*

17
18 274 Patients recruited at the coordinating centre (Bellvitge University Hospital) will be included in a
19
20 275 pharmacological sub-study, after obtaining additional signed informed consent. The variables
21
22 276 assessed will be:

- 23
24
25 277 - Minimum and maximum concentration in steady state of fosfomycin and cloxacillin,
26
27 278 and pharmacokinetic variability of these concentrations.
28
29 279 - Associations between pharmacokinetic parameters and efficacy.
30
31

32 280

33
34 281 *Safety:*

35
36 282 Safety of cloxacillin plus fosfomycin as compared with cloxacillin alone (See Supplementary
37
38 283 material).
39

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43 285 **Follow-up and data collection**

44
45 286 During the first week of treatment, all patients will be assessed at days 1, 3 and 7 by a member
46
47 287 of the investigating team, and followed up daily by an infectious diseases specialist. Scheduled
48
49 288 visits are reported in Table 2. A follow-up visit will be arranged for all participants at EOT (48h
50
51 289 after the last dose of antibiotic treatment) and at TOC. At this last visit, a structured telephone
52
53 290 interview will be performed to assess outcomes.
54
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3 291 All data will be recorded on a secure web application used for building and managing online
4
5 292 databases (REDCap). Authorised staff will be free to examine the records for quality assurance
6
7 293 and audit purposes.
8
9

10 294

11 295 **Endpoint assessment**

12
13
14 296 The primary endpoints will be assessed by a committee comprising three independent senior
15
16 297 infectious disease specialists with extensive experience in *S. aureus* bacteraemia and
17
18 298 endocarditis. This committee will be blinded to treatment allocation and to patient
19
20 299 identification. Committee members will receive a data extract containing patients'
21
22 300 demographical data, comorbidities, source of infection, quick SOFA score at baseline and day
23
24 301 7, date and results of blood and sterile cultures between randomisation and TOC, as well as
25
26 302 date of death if applicable.
27
28
29

30 303

31 304 **Statistical analysis plan**

32 305 *Sample size*

33
34
35 306 Prior data indicate a success rate in the cloxacillin alone group of 74% [4]. To achieve a success
36
37 307 rate in the experimental group of 86% (i.e., an absolute difference of 12%, considered as
38
39 308 clinically significant) we will need 183 experimental subjects and 183 control subjects to reject
40
41 309 the null hypothesis of an equal success rate with a probability of 80%. The probability of type I
42
43 310 error associated with this test is 5%, and a drop-out rate of 5% has been anticipated.
44
45
46

47 311 *Allocation*

48
49 312 Participants will be block randomised to receive monotherapy or combination using an
50
51 313 internet-based, concealed computer-generated random allocation sequence. Random blocks
52
53 314 will be of size 4 or 6. The randomised sequence allocation will be stored in the Biostatistics
54
55 315 Unit at Biomedical Research Institute of Bellvitge (IDIBELL) and will not be available to any
56
57 316 member of the research team.
58
59
60

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2
3 317 *Data analysis*
4

5 318 The main analysis will be performed for the intention to treat population, which will include all
6
7 319 randomised patients included in the study with a primary outcome assessment. If no statistical
8
9 320 significance is detected by day 7 in the hierarchy, then no further hypothesis testing will be
10
11 321 performed. The analysis will be repeated in the per protocol population. All patients who
12
13 322 receive at least one dose of treatment will be included in the safety analysis.
14
15

16 323 The Chi-square test will be used to test the binary endpoints of the success rate. The relative
17
18 324 risk for success rate will be calculated, accompanied by 95% confidence intervals. Absolute risk
19
20 325 difference and 95% confidence interval will also be reported. The time-to-event outcomes,
21
22 326 including the time of response, and overall survival will be estimated using the Kaplan-Meier
23
24 327 method [24]. To account for competing risks, cause-specific cox regression models will be
25
26 328 used, and event cause cumulative incidence functions will be plotted [25]. All analyses and
27
28 329 data management will be performed with R software, version 4.0.4 or superior [26].
29
30

31
32 330

33
34 331 **Monitoring**

35
36 332 *Monitoring plans*
37

38
39 333 The data monitoring board will ensure the correct progress of the study in terms of safety, and
40
41 334 also the sample size assumptions.
42

43 335 *Harms - Data Safety and Monitoring Board (DSMB)*
44

45 336 An independent DSMB will review safety data and provide advice about the continuation,
46
47 337 modification and/or termination of the study, as well as adherence to the protocol,
48
49 338 recruitment, outcomes and additional data related to participants' safety. The DSMB will be
50
51 339 composed by specialists in pharmacology, biostatistics and infectious diseases. The review by
52
53 340 the DSMB will be performed when half of the sample size will be reached.
54
55

56 341 *Adverse events reporting and quantification*
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58
59
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1
2
3 342 An adverse event will be defined as any injury related to medical management occurring
4
5 343 during the patient's participation in the study, even if it is not related to the study medication.

6
7 344 An adverse drug event will be defined as any medication-related adverse event occurring
8
9 345 during the patient's participation in the clinical trial.

10
11 346 An adverse drug reaction will be defined as any 'adverse drug event' occurring when the
12
13 347 medication is used as directed and at the usual dosage.

14
15 348 Serious adverse event or reaction will be defined as an event or reaction that:

- 16
17
18 349 - Results in death;
19
20 350 - Is life-threatening;
21
22 351 - Causes persistent or significant disability;
23
24 352 - Causes a congenital anomaly/birth defect;
25
26 353 - Requires in-patient hospitalisation or prolongation of existing hospitalisation (not
27
28 354 related to basal diseases).

29
30 355 *Adverse drug events of particular interest for the study*

31
32 356 - Hypokalaemia and hypocalcaemia: blood analysis will be performed every 2-3 days
33
34 357 during the first week to permit potassium and calcium control. Furthermore,
35
36 358 administration of potassium supplement will be recommended from the first day of
37
38 359 treatment to avoid this complication.

39
40 360 - Sodium overload: since both fosfomycin and cloxacillin carry a high sodium load, daily
41
42 361 physical examination and administration of a low dose of a diuretic such as furosemide
43
44 362 will be recommended to avoid hypertension, oedema and acute cardiac failure.

45
46 363 *Reporting*

47
48 364 Any adverse events occurring during the patient's participation in the clinical trial will be
49
50 365 recorded on the clinical chart by the principal investigator at each scheduled visit. The principal
51
52 366 investigator will record its possible relationship to the study drug.
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3 367 The electronic case report form should record only the following: serious adverse drug events;
4
5 368 adverse events (of any degree) related to the study medication, in the opinion of the PI;
6
7 369 adverse events (of any degree) leading to modification of the dosage of the study drug or its
8
9
10 370 interruption/early discontinuation; adverse events of particular interest for the study.

11
12 371 The sponsor will be notified of all serious adverse events within 24 h of their occurrence.
13
14 372

15
16 373 **Trial status**

17
18 374 The SAFO trial opened its first recruitment site on 31 May 2019. The first patient was enrolled
19
20 375 on 1 July 2019. Follow up is expected to be completed by May 2022.
21
22 376

23
24
25 377 **Declaration**

26
27 378 *Ethics*

28
29 379 The trial will be conducted in accordance with the principles of the most recent Declaration of
30
31 380 Helsinki (agreed by the 64th World Medical Association General Assembly in 2013), the Good
32
33 381 Clinical Practice (GCP) guidelines, and the current local legislation.

34
35 382 The study was authorised by the Spanish Medicines and Healthcare Products Regulatory
36
37 383 Agency (AEMPS, 18-0905) and by the Bellvitge University Hospital Ethics committee
38
39 384 (AC069/18).

40
41 385 The principal investigator or collaborator at each site will provide patients with the information
42
43 386 sheet, and s/he will explain the nature of the study and the objectives and clarify any doubts.

44
45 387 Written informed consent will be obtained from all patients or from their legal representatives
46
47 388 (LRs) if they lack capacity, before enrolment (Supplementary file). Patients (or their LRs) are
48
49 389 free to withdraw from the trial at any time; this will be explicitly stated on the patient's
50
51 390 information sheet.

52
53 391 Patients' personal and clinical information will be managed in accordance with European
54
55 392 Regulation 2016/679 and Spanish legislation. The trial protocol was approved by the research
56
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3 393 ethics committee on 28 March 2019 and by the AEMPS on 8 April 2019. The informed consent
4
5 394 form and information sheet were approved by the research ethics committee on 28 March
6
7 395 2019. The emendation regarding “acude SARS-CoV2 infection” as exclusion criteria was
8
9 396 approved by the research ethics committee and by the AEMPS on 29 November 2020.

11
12 397 *Data sharing plan and dissemination*

13
14 398 Sharing of data generated by this project is an essential part of our proposed activities and will
15
16 399 be carried out in several different ways. We would wish to make our results available both to
17
18 400 the community of scientists interested in infectious diseases and the biology of *Staphylococcus*
19
20 401 *aureus* to avoid unintentional duplication of research.

21
22
23 402 The preliminary results will be presented at international and national infectious diseases
24
25 403 conferences and will be published in peer-reviewed journals. The results will also be made
26
27 404 available to patients, caregivers and funders through press and social media communications.

28
29
30 405 A corporative *Twitter* account will be created to establish direct contact with the general
31
32 406 public and other health-care professionals. Any formal presentation or publication of data
33
34 407 collected from this study will be considered as a joint publication by the participating
35
36 408 investigators and will follow the recommendations of the International Committee of Medical
37
38 409 Journal Editors (ICMJE).

39
40
41 410 Individual participant data that underlie the results, after deidentification (text, tables, figures,
42
43 411 and appendices) will be available immediately following publication and ending 5 years
44
45 412 following article publication. Data will be shared with researchers who provide a
46
47 413 methodologically sound proposal to achieve aims in the approved suggestions. Propositions
48
49 414 should be directed to the corresponding author.

50
51
52 415 *Patients and public involvement*

53
54 416 Patients will not be involved in either the enrolment or the execution of the trial, or in the
55
56 417 assessment of the interventions. However, before the beginning of the study, a number of
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2
3 418 patients with previous *S. aureus* bacteraemia were contacted by phone to obtain their
4
5 419 feedback about the study.
6

7 420

9 421 **Protocol amendments**

11 422 No protocol modifications will become effective until approved by the relevant authorities and
12
13 423 by the Drug Research Ethics Committee (CEIm). Exceptions will be made for any changes to
14
15 424 protect patients from imminent harm and those concerning exclusively logistic or
16
17 425 administrative aspects.
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For peer review only

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3 508 *Authors' contributions*
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6 509 SG, GC, JM, JC, DB, MD, AP, SC and MP conceived and designed the study. SG, GC, MP and JC
7
8 510 wrote and revised the manuscript. CT and NP designed and wrote statistical analysis plan. PH
9
10 511 and SV critically reviewed the protocol. SG, GC, RSJ, JA, LM, SGZ, JLC, OG, AGG, SI, GGP, EC,
11
12 512 LBP, IO, AJS, LELC, GE, MA, MJGP, FG, JRP, MLPB, RB, MTPR, YM, MBLV and GH will contribute
13
14 513 to the acquisition of data. All authors have read and approved the final manuscript.
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18 514 *Trial sponsor:* Miquel Pujol, MD PhD. Department of Infectious Diseases, Hospital Universitari
19
20 515 de Bellvitge, Institut Investigacions Biomèdiques de Bellvitge (IDIBELL), Carrer de la Feixa
21
22 516 Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona. Tel.: +34. 93 2602487
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26 517 *Funding statement*
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28
29 518 The SAFO trial is supported by a competitive grant awarded by the Fondo de Investigaciones
30
31 519 Sanitarias at the Spanish government's National Institute of Health Research, Instituto de Salud
32
33 520 Carlos III (ISCIII), (FIS PI17/01116). This study was supported by Plan Nacional de I+D+i 2017–
34
35 521 2021 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de
36
37 522 Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish
38
39 523 Network for Research in Infectious Diseases (REIPI RD16/0016/0005).
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47
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49
50 527 for technical help.
51

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53 528 *Competing interests*
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56 529 GH received a research grant from ERN (19PNJ145).
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60 530 *List of abbreviation*

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3 531 MSSA: Methicillin-susceptible *Staphylococcus aureus* bacteraemia. TOC: test of cure. SPIRIT:
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5 532 Standard Protocol Items: Recommendation for Interventional Trials. CONSORT: Consolidated
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7 533 Standards of Reporting Trials. SOFA: Sequential Organ Failure Assessment. MRSA: Methicillin-
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9 534 resistant *Staphylococcus aureus*. EOT: End of Treatment. GCP: Good Clinical Practice.
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535 **Tables**536 **Table 1.** Fosfomycin dosage adjusted to renal function.

Creatinine clearance (mL/min)	Fosfomycin dosage
>40	3 g every 6 hours
20-40	3 g every 12 hours
10-20	3g every 24 hours
<10	3 g every 48 hours
Haemodialysis	3 g after haemodialysis
Continuous renal replacement therapy	3 g every 24 hours

537 Abbreviations: mL: millilitre; min: minute.

538 **Table 2.** The SAFO evaluation schedule.

	Visit				Unscheduled			
	Day	Screening	0	3	7	EOT	Visit ¹	TOC
All patients								
Eligibility criteria		X						
Pregnancy test ²		X						
Informed consent		X						
Randomisation			X					
Clinical evaluation			X	X	X	X	X	X ³
Quick SOFA score			X		X			
Blood cultures			X	X	X	X	X	X ³
Blood count and biochemical analysis ⁴			X	X	X		X	X ³
Adverse events record				X	X	X	X	X
Concomitant medication			X	X	X	X		
Subgroup of patients with PK/PD sub analysis								
Lithium heparin blood sample (2x 5mL)					X			

539 ¹Unscheduled visit will be performed only in case of clinical infectious symptoms and signs.

540 ²Pregnancy test will be performed only in woman of childbearing age.

541 ³In absence of infective symptoms, clinical assessment may be made by phone call; blood culture and
542 blood analysis will not be necessary.

543 ⁴Complete blood count, biochemical analysis (C-reactive protein-, creatinine, urea, creatinine clearance,
544 AST, ALT, bilirubin, sodium, potassium, calcium, acid-base analysis) and coagulation test (prothrombin
545 test/INR).

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546 **Figures**

547 **Figure 1.** Study design.

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551 **Supplementary material**

552 **List of study sites:** Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona;
553 Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona;
554 Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona;
555 Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mútua de Terrassa,
556 Barcelona; Corporació Sanitaria Parc Taulí, Sabadell, Barcelona; Hospital Universitari Sant Joan,
557 Reus; Hospital Universitario M.Broggi, Sant Joan Despí, Barcelona; Hospital Universitario 12 de
558 Octubre, Madrid; Hospital Universitario Virgen Macarena, Seville; Hospital Universitario de
559 Cruces, Barakaldo; Hospital Universitario Lucus Augusti, Lugo; Hospital Clínico Universitario de
560 Zaragoza, Zaragoza; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitari
561 Germans Trias, Badalona; Hospital Universitario Álvaro Cunqueiro, Vigo; Hospital de Barcelona,
562 Barcelona; Hospital Universitario La Paz, Madrid.
563 Other hospitals may be added during the course of the clinical trial.

564

565 **Microbiological studies**

566 In fosfomicin resistant SASM strains, synergy studies between cloxacillin and fosfomicin will be
567 assessed by E-test and time-kill assays.

568 For the time-kill assays 0.25, 0.5 and 1 fold MIC for each antibiotic will be tested. Synergy for
569 the combination is defined as $>2 \log_{10}$ CFU/mL decrease in comparison with that by the most
570 active antibiotic of the combination tested, and antagonism is defined as $>2 \log_{10}$ CFU/mL
571 increase.

572 For the E-test, we calculate the fractional inhibitory concentration index (FICI) with the
573 following formula: $FICI = (MICCF/MICC) + (MICBFC/MICF)$, where MICCF is the MIC of cloxacillin
574 tested in combination with fosfomicin, MICC and MICF are the MIC of cloxacillin and
575 fosfomicin tested alone, MICFC is the MIC of fosfomicin tested in combination with cloxacillin.
576 Synergy is defined as a $FICI \leq 0.5$, indifference as a $FICI$ between >0.5 and 4 and antagonism as a

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7 579 **Safety outcomes**
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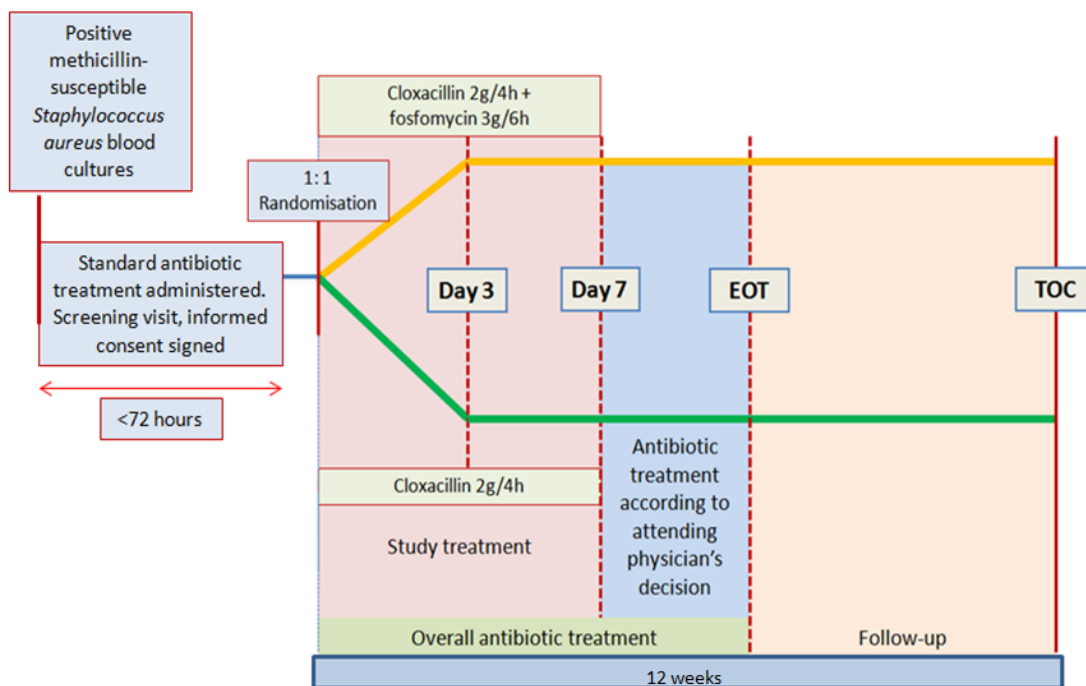
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18 584 Additional ethical information
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35 592 accordance with the current legislation.
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HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

EudraCT num.: 2018-001207-37

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge

Investigador principal:

Centro:

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por el Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir.

Además, puede consultar con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

OBJETIVO DEL ESTUDIO

La bacteriemia por *Staphylococcus aureus*, que es la enfermedad que usted padece ahora, es una infección muy frecuente y que presenta una elevada mortalidad. El tratamiento actual es la Cloxacilina como único fármaco.

El objetivo es establecer si añadir otro antibiótico (Fosfomicina) al tratamiento habitual con Cloxacilina mejora el pronóstico de esta infección.

HOJA DE INFORMACIÓN AL PACIENTE

DESCRIPCIÓN DEL ESTUDIO

El presente estudio prevé la inclusión de 366 pacientes y se realizará en 15 diferentes hospitales en toda España.

Tanto la Cloxacilina como la Fosfomicina son fármacos que ya están comercializados y se utilizan en la práctica clínica habitual.

El estudio pretende que algunos pacientes además de recibir el tratamiento con cloxacilina (que es el tratamiento habitual de esta infección) reciban también otro antibiótico asociado, la fosfomicina. La combinación de estos dos antibióticos pretende mejorar el control de la infección y así disminuir las complicaciones que esta infección comporta.

Los pacientes recibirán el tratamiento de estudio o el tratamiento habitual. El que Usted reciba el tratamiento de estudio (Cloxacilina + Fosfomicina) o el tratamiento habitual (Cloxacilina sola) será determinado por el azar a través de una asignación por un programa informático. Usted tiene la misma probabilidad que le toque uno u otro tratamiento.

Por el diseño del estudio, tanto su médico habitual como usted sabrán en todo momento que medicación está recibiendo. La medicación será administrada por vía intravenosa.

ACTIVIDADES DEL ESTUDIO

El tratamiento de estudio durará 7 días, después de los cuales el tipo de tratamiento y la duración serán decididos por su médico habitual según la práctica clínica habitual. El seguimiento será de 12 semanas después del comienzo del tratamiento.

Si acepta participar en el estudio, además de las visitas que realizará su equipo médico habitual, se le realizarán 5 visitas extras (el primero, tercero y séptimo día de tratamiento, al final del tratamiento total y después de 12 semanas desde el comienzo del tratamiento). En caso que usted lo necesite (si presentara fiebre por ejemplo) se le realizará una visita extra entre la visita 4 y la visita 5.

Durante las visitas de la 1 a la 5, y en la visita extra si lo requiriese, el equipo investigador realizará una evaluación clínica que incluirá ver si tiene fiebre, conocer su tensión arterial y exploración física general. Comprobará también los resultados de análisis de sangre (hemograma, función renal y hepática, iones y equilibrio ácido-base venoso) que le haya realizado su equipo médico ese día.

También durante todas las visitas se solicitarán 2 muestras de sangre de 10 mL (hemocultivos) para asegurar que la bacteria que le ha producido la enfermedad ha desaparecido de su sangre.

Durante el estudio no se le realizarán analíticas complementarias a las que se realizan en la práctica habitual de su enfermedad.

Las muestras obtenidas se utilizaran para los análisis del estudio, pero no se prevé su almacenamiento una vez concluidos los análisis del estudio.

HOJA DE INFORMACIÓN AL PACIENTE Visita 1	Visita 2	Visita 3	Visita 4	Visita 5
Día de la inclusión	Día +3 desde inicio tratamiento del estudio	Día + 7 desde inicio tratamiento del estudio	A las 48 h de la finalización del ciclo de tratamiento antibiótico completo	+ 12 semanas de la asignación aleatoria
Exploración física	Exploración física	Exploración física	Exploración física	Exploración física
Test de embarazo				
Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)
En caso de fiebre o síntomas de infección entre la visita 4 y la visita 5, se realizará una visita extraordinaria donde se le realizará una exploración física y se obtendrán muestras de sangre.				

RIESGOS Y MOLESTIAS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Los fármacos utilizados en este estudio están autorizados para el tratamiento de la enfermedad que Usted padece. Están comercializados desde hace muchos años y se utilizan en la práctica clínica habitual.

Los efectos secundarios principales que pueden presentarse con ambos fármacos son la sobrecarga de sodio y la posibilidad de un descenso del potasio. La sobrecarga de sodio, podría desencadenar episodios de insuficiencia cardíaca y será valorada en las visitas y se administrará tratamiento diurético cuando sea necesario. La hipokalemia (descenso del potasio en sangre), se puede corregir con la administración de potasio a través de sueros o por vía oral. Ambas eventualidades serán valoradas y se realizarán controles y medidas para evitar su desarrollo. Otros efectos secundarios descritos con la fosfomicina son: reacciones cutáneas por hipersensibilidad, aumento transitorio de los enzimas hepáticos, náuseas, diarreas, hipocalcemia (descenso de calcio en sangre) y alcalosis metabólica.

Al ser, tanto la cloxacilina como la fosfomicina, fármacos aprobados por las autoridades sanitarias competentes, existe información al acceso de todo el mundo sobre los efectos secundarios. Por favor, hable con el médico de su estudio para obtener una lista completa de los efectos secundarios comunicados con este fármaco y en cualquier caso se le entregará el prospecto del fármaco.

Si acepta participar al estudio, acepta acudir a las visitas de seguimiento y de notificar cualquier evento adverso que le suceda o cambios en medicación, advirtiéndole que, excepto en caso de urgencia, no modifique la medicación que está tomando ni tome otros medicamentos o "plantas medicinales" sin consultar antes con el médico del estudio.

HOJA DE INFORMACIÓN AL PACIENTE

Todos los procedimientos que se realizarán durante el ensayo clínico son procedimientos habituales de la práctica clínica. La participación al ensayo supone la extracción de muestras de sangre (hemocultivos) en diferentes momentos, que no difiere de la práctica clínica habitual. Este procedimiento, aunque de bajo riesgo, en ocasiones puede producir hemorragias, hematomas, molestias, infecciones y/o dolor en el punto de extracción de sangre. También puede sentirse mareado.

Los posibles riesgos derivados del procedimiento realizado para la obtención de estas muestras estarán cubiertos por la póliza del seguro del centro hospitalario.

La realización de pruebas diagnósticas (pruebas de imagen o de obtención de muestras clínicas) o terapéuticas invasivas (drenaje de material purulento, desbridamiento quirúrgico), se realizarán según la práctica clínica habitual. La participación al presente ensayo no supone realizar más pruebas de las necesarias.

POSIBLES BENEFICIOS

El posible beneficio de su participación en el estudio es la mejora del tratamiento de la patología en los futuros pacientes. De todas maneras, es posible que no obtenga ningún beneficio para su salud por participar en este estudio.

ADVERTENCIA RELATIVA AL EMBARAZO

Se realizará un test de embarazo antes del comienzo del estudio en las mujeres en edad fértil. Los fármacos empleados en este estudio deben evitarse durante el embarazo. No hay literatura que haya demostrado toxicidad fetal en caso de uso de Cloxacilina. Para lo que concierne la Fosfomicina, se ha demostrado toxicidad para el feto en animales sólo a dosis que provocarían toxicidad materna.

En caso de producirse un embarazo durante su participación en el estudio debe informar a su médico de inmediato para recibir la asistencia médica adecuada. Se solicitará el consentimiento de la recogida de datos del mismo y de datos de salud del bebé hasta 3 meses después (Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales).

TRATAMIENTOS ALTERNATIVOS

No existen actualmente tratamientos alternativos que hayan demostrado la superioridad respecto al tratamiento habitual con Cloxacilina. Dada la elevada mortalidad de la enfermedad, en la práctica clínica habitual se utilizan diferentes combinaciones de tratamiento, sin que éstas hayan demostrado ser más eficaces que el tratamiento de la cloxacilina sola. Si el paciente decide no participar en el estudio, podría recibir esta misma combinación u otro tratamiento.

HOJA DE INFORMACIÓN AL PACIENTE

SEGURO

Para la participación en este estudio Usted estará cubierto por la póliza de seguro de cada centro hospitalario. No está previsto contratar un seguro específico.

Le informamos que es posible que su participación en este ensayo clínico pueda modificar las condiciones generales y particulares (cobertura) de sus pólizas de seguros (vida, salud, accidente), por ello, le recomendamos que se ponga en contacto con su compañía de seguros y le informe de su participación en el mismo para determinar si podría afectar a su póliza de seguro actual o en el caso de que vaya a contratar una póliza nueva.

PROTECCIÓN DE DATOS PERSONALES

Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen al cumplimiento del Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD), así como al resto de leyes y normativa vigente y aplicable (Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales).

Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle (nombre ni apellidos, iniciales, dirección, nº de la seguridad social, etc), sino un código. El código que le identifica será asignado de manera aleatoria a través de un programa informático. Sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica.

Las muestras biológicas del estudio también estarán identificadas por su código asignado en el estudio acompañado del código de la visita, cumpliendo con lo expuesto en el párrafo anterior.

Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección (Agencia Española de Medicamentos y Productos Sanitarios, autoridades sanitarias extranjeras) y el personal autorizado por el Promotor (monitores, auditores), únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en esta ley.

De acuerdo a lo que establece la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio. Además también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador

Versión 4.0 del 10 de junio de 2020

HOJA DE INFORMACIÓN AL PACIENTE

principal del estudio o al Delegado de protección de datos de la institución, email: dataprotection@idibell.cat.

Si usted decide retirar el consentimiento para participar en este estudio, ningún nuevo dato será añadido a la base de datos, pero los datos que ya se hayan recogido hasta el momento no se podrán eliminar para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello y si así lo permite la ley y requisitos éticos aplicables.

Si se realizara una transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al/ a la Delegado de Protección de Datos del promotor [secretariaserveiiinfecciosos@bellvitgehospital.cat]

GASTOS Y COMPENSACIÓN

En caso de participar en este estudio, usted no tendrá ningún gasto adicional ocasionado por el estudio. No está prevista ninguna compensación económica por participar en el estudio.

OTRA INFORMACIÓN RELEVANTE

Una descripción de este ensayo clínico estará disponible en <http://reec.aemps.es>, según exige la legislación española. Cualquier nueva información referente a los fármacos utilizados en el estudio y que pueda afectar a su disposición para participar en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible.

Debe saber que puede ser excluido del estudio si el promotor o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca por la medicación en estudio o porque

consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio.

Al firmar la hoja de consentimiento adjunta, acepta cumplir con los procedimientos del estudio que se le han expuesto.

HOJA DE INFORMACIÓN AL PACIENTE

Debe usted saber que es posible que su médico de Atención Primaria tenga conocimiento de su participación en este estudio.

¿QUÉ TRATAMIENTO RECIBIRÉ CUANDO FINALICE EL ENSAYO CLÍNICO?

Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere el más adecuado para su enfermedad, pero es posible que no se le pueda seguir administrando la medicación del estudio. Por lo tanto, ni el investigador ni el promotor adquieren compromiso alguno de mantener dicho tratamiento fuera de este estudio.

CONTACTO EN CASO DE DUDAS

Si durante su participación tiene alguna duda o necesita obtener más información, póngase en contacto con Dr/a _____
y teléfono _____.

CONSENTIMIENTO INFORMADO

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus Cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge.

Investigador Principal:

Centro:

Yo (nombre y apellidos): _____

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: _____ (nombre del investigador)
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio cuando quiera, sin tener que dar explicaciones, sin que esto repercuta en mis cuidados médicos.
- Acepto que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.
Presto libremente mi conformidad para participar en el estudio.

Firma del participante
Fecha: ____/____/____
(Nombre, firma y fecha de puño y letra por el paciente)

Firma del investigador
Fecha: ____/____/____

Cuando se obtenga el CI en personas con capacidad modificada para dar su CI.

Firma del representante legal, familiar o
persona vinculada de hecho
Fecha: ____/____/____
(Nombre, firma y fecha de puño y letra por el representante)

Firma del investigador
Fecha: ____/____/____

CONSENTIMIENTO INFORMADO ORAL ANTE TESTIGOS

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus Cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge.

Investigador Principal:

Centro:

Yo, _____ (*nombre y apellidos del testigo*),
como testigo, afirmo que en mi presencia se ha informado a D/D^a
_____ (*nombre y apellidos del participante*) y se
ha leído la hoja de información que se le ha entregado sobre el estudio, de modo que:

- Ha podido hacer preguntas sobre el estudio.
- Ha recibido suficiente información sobre el estudio.
- Ha hablado con: _____ (*nombre del investigador*)
- Comprende que su participación es voluntaria.
- Comprende que puede retirarme del estudio cuando quiera, sin tener que dar explicaciones, sin que esto repercuta en sus cuidados médicos.
- Acepta que le comuniquen la información derivada de la investigación que pueda ser relevante para su salud.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Firma del testigo

Fecha: ____/____/____

(Nombre, fecha y firma de puño y letra por el paciente/testigo)

Firma del investigador

Fecha: ____/____/____

CONSENTIMIENTO INFORMADO ORAL ANTE TESTIGOS

El participante del estudio ha indicado que no puede leer /escribir.

Un miembro del personal del estudio le ha leído el documento de consentimiento, lo ha revisado y comentado con el participante y se le ha concedido la oportunidad de hacer preguntas o consultarlo con otras personas.

El testigo ha de ser una persona imparcial, ajena al estudio.

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

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	21
	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	12
	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)	12
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	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
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)	8

Methods: Participants, interventions, and outcomes

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	8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	10
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)	23
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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	13
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	13
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	12
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13				
14				
15		17b	If blinded, circumstances under which unblinding is permissible, and	NA
16			procedure for revealing a participant's allocated intervention during	
17			the trial	
18				
19				

Methods: Data collection, management, and analysis

20				
21				
22	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	12
23	methods		trial data, including any related processes to promote data quality (eg,	
24			duplicate measurements, training of assessors) and a description of	
25			study instruments (eg, questionnaires, laboratory tests) along with	
26			their reliability and validity, if known. Reference to where data	
27			collection forms can be found, if not in the protocol	
28				
29				
30		18b	Plans to promote participant retention and complete follow-up,	
31			including list of any outcome data to be collected for participants who	
32			discontinue or deviate from intervention protocols	
33				
34	Data	19	Plans for data entry, coding, security, and storage, including any	12
35	management		related processes to promote data quality (eg, double data entry;	
36			range checks for data values). Reference to where details of data	
37			management procedures can be found, if not in the protocol	
38				
39				
40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	13
41	methods		Reference to where other details of the statistical analysis plan can be	
42			found, if not in the protocol	
43				
44				
45		20b	Methods for any additional analyses (eg, subgroup and adjusted	12
46			analyses)	
47				
48		20c	Definition of analysis population relating to protocol non-adherence	13
49			(eg, as randomised analysis), and any statistical methods to handle	
50			missing data (eg, multiple imputation)	
51				

Methods: Monitoring

52				
53				
54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	14
55			and reporting structure; statement of whether it is independent from	
56			the sponsor and competing interests; and reference to where further	
57			details about its charter can be found, if not in the protocol.	
58			Alternatively, an explanation of why a DMC is not needed	
59				
60				

1				
2		21b	Description of any interim analyses and stopping guidelines, including	14
3			who will have access to these interim results and make the final	
4			decision to terminate the trial	
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and	14
7			spontaneously reported adverse events and other unintended effects	
8			of trial interventions or trial conduct	
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and	15
12			whether the process will be independent from investigators and the	
13			sponsor	
14				
15				
16	Ethics and dissemination			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board	15
18	approval		(REC/IRB) approval	
19				
20	Protocol	25	Plans for communicating important protocol modifications (eg,	17
21	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties	
22			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
23			regulators)	
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial	15
27			participants or authorised surrogates, and how (see Item 32)	
28				
29		26b	Additional consent provisions for collection and use of participant data	12
30			and biological specimens in ancillary studies, if applicable	
31				
32	Confidentiality	27	How personal information about potential and enrolled participants will	15
33			be collected, shared, and maintained in order to protect confidentiality	
34			before, during, and after the trial	
35				
36				
37	Declaration of	28	Financial and other competing interests for principal investigators for	21
38	interests		the overall trial and each study site	
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and	16
41			disclosure of contractual agreements that limit such access for	
42			investigators	
43				
44				
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	
46	post-trial care		compensation to those who suffer harm from trial participation	
47				
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	16
49	policy		participants, healthcare professionals, the public, and other relevant	
50			groups (eg, via publication, reporting in results databases, or other	
51			data sharing arrangements), including any publication restrictions	
52				
53		31b	Authorship eligibility guidelines and any intended use of professional	
54			writers	
55				
56		31c	Plans, if any, for granting public access to the full protocol, participant-	16
57			level dataset, and statistical code	
58				
59				
60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if 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.

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BMJ Open

Multicentre, randomised, open-label, phase IV-III study to evaluate the efficacy of cloxacillin plus fosfomicin versus cloxacillin alone in adult patients with methicillin-susceptible *Staphylococcus aureus* bacteraemia: study protocol for the SAFO trial.

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6 2 **efficacy of cloxacillin plus fosfomycin versus cloxacillin alone in adult**
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14 5 Sara Grillo, Guillermo Cuervo, Jordi Carratalà, Rafael San-Juan, José Maria Aguado, Laura
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34 41 **Pedro-Botet PhD, RM Benítez MD); Department of Infectious Diseases, Hospital Clínico**
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36 42 **Universitario Lozano Blesa, Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain (JR**
37
38 43 **Paño-Pardo PhD); Department of Internal Medicine, Hospital Universitario Moisés Broggi,**
39
40 44 **Sant Joan Despí, Spain (I Oriol PhD); Department of Infection and Immunity, Hospital**
41
42 45 **Universitari Sant Joan de Reus, Reus, Spain (SM Iftimie MD), Department of Infectious**
43
44 46 **Diseases and Internal Medicine, Hospital Álvaro Cunqueiro, Complejo Hospitalario**
45
46 47 **Universitario de Vigo, Spain (MT Perez-Rodríguez MD), Infectious Disease Unit. Internal**
47
48 48 **Medicine Department. Hospital de Barcelona. Societat Cooperativa d'Instal·lacions**
49
50 49 **Assistencials Sanitàries (SCIAS). Barcelona, Spain (Y. Meije MD), Department of Infectious**
51
52 50 **Diseases, Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario de La**
53
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30 68

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2
3 **70 Abstract**
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5
6 **71 Introduction:**
7

8 Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia is a frequent condition,
9
10 with high mortality rates. There is a growing interest in identifying new therapeutic regimens
11
12 able to reduce therapeutic failure and mortality observed with the standard of care of beta-
13
14 lactam monotherapy. *In vitro* and small-scale studies have found synergy between cloxacillin
15
16 and fosfomycin against *S. aureus*. Our aim is to test the hypothesis that cloxacillin plus
17
18 fosfomycin achieves higher treatment success than cloxacillin alone in patients with MSSA
19
20 bacteraemia.
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23
24 **79 Methods:**
25

26 We will perform a superiority, randomised, open-label, phase IV-III, two-armed parallel group
27
28 (1:1) clinical trial at 20 Spanish tertiary hospitals. Adults (≥ 18 years) with isolation of MSSA
29
30 from at least one blood culture ≤ 72 hours before inclusion with evidence of infection, will be
31
32 randomly allocated to receive either cloxacillin 2g/4h intravenous (IV) plus fosfomycin 3 g/6h
33
34 IV or cloxacillin 2g/4h IV alone for seven days. After the first week, sequential treatment and
35
36 total duration of antibiotic therapy will be determined according to clinical criteria by the
37
38 attending physician.
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40

41 Primary endpoints: 1) Treatment success at day 7, a composite endpoint comprising all the
42
43 following criteria: patient alive, stable or with improved quick-SOFA score, afebrile and with
44
45 negative blood cultures for MSSA at day 7. 2) Treatment success at Test of Cure visit (TOC):
46
47 patient alive and no isolation of MSSA in blood culture or at another sterile site from day 8
48
49 until TOC (12 weeks after randomisation).
50
51

52 We assume a rate of treatment success of 74% in the cloxacillin group. Accepting alpha risk of
53
54 0.05 and beta risk of 0.2 in a two-sided test, 183 subjects will be required in each of the control
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56 and experimental groups to obtain statistically significant difference of 12% (considered
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58 clinically significant).
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97 **Ethics and dissemination:** Ethical approval has been obtained from the Ethics Committee of
98 Bellvitge University Hospital (AC069/18) and from the Spanish Medicines and Healthcare
99 Product Regulatory Agency (AEMPS, AC069/18), and is valid for all participating centres under
100 existing Spanish legislation. The results will be presented at international meetings and will be
101 made available to patients and funders.

102 The protocol has been approved by AEMPS with the Trial Registration Number EudraCT 2018-
103 001207-37. ClinicalTrials.gov Identifier: NCT03959345.

104

105 **Strengths and limitations of this study**

106 - The primary endpoints are strong composite outcomes that will assess mortality, clinical and
107 microbiological failure at 7 and 90 days after randomisation.

108 - The multicentre nature of the study supports the generalisability of the results.

109 -A blinded adjudication committee will evaluate the key study endpoints and mitigate the
110 observer bias inherent in the open-label design.

111 - Given the increased risk of sodium overload, patients with cardiac failure and hepatic
112 cirrhosis will be excluded.

113 Introduction

114 *Staphylococcus aureus* is one of the most common causes of bacteraemia and endocarditis in
115 industrialised countries, and has particularly high hospitalisation and mortality rates (and
116 associated costs) [1,2]. Healthcare exposure and the increasing use of invasive devices have
117 contributed to the high burden of the disease [3].

118 Mortality rates at 90 days due to methicillin-susceptible *Staphylococcus aureus* (MSSA)
119 bacteraemia range between 20 and 30% [4][5]. Mortality has been linked to factors such as
120 age, co-morbidities, source of infection, pathogen virulence elements and optimisation of
121 antibiotic treatment [6]. Complicated *S. aureus* bacteraemia is common, and is an indicator of
122 poor prognosis [7]. Indeed, every continued day of bacteraemia has been associated with a
123 higher risk of mortality [8][9].

124 Although MSSA bacteraemia is a common and life-threatening infection, it is still unclear
125 whether combination therapy can reduce duration of bacteremia or reduce mortality
126 compared with the current standard of care (monotherapy beta-lactams). For over 50 years,
127 the standard treatment of MSSA bacteraemia has been antistaphylococcal penicillin
128 monotherapy [10]. Today, there is a growing interest in identifying new therapeutic regimens
129 able to reduce the rate of therapeutic failure and improve the outcomes obtained with the
130 standard of care.

131 Strategies combining cloxacillin with aminoglycosides have not shown any significant
132 improvement in patients' outcomes, and have been associated with a higher risk of
133 nephrotoxicity [11]. A randomised multicentre study conducted in the UK, which included
134 around 1000 patients and compared the efficacy of the rifampicin combination with the
135 standard treatment for *S. aureus* bacteraemia, did not show a reduction in early or late
136 mortality for the combined therapy compared with monotherapy [12]. Nor did two recent
137 studies comparing a beta-lactam and daptomycin combination with beta-lactams in

1
2
3 138 monotherapy to treat MSSA bacteraemia show any differences in mortality between groups
4
5 139 [13][4].

6
7 140 Among the combinations that might improve the outcome of patients with MSSA bacteraemia,
8
9 141 cloxacillin plus fosfomycin is an appealing strategy. Fosfomycin is a bactericidal antibiotic
10
11 142 which inhibits synthesis of N-acetylmuramic acid, a precursor of bacterial wall peptidoglycan,
12
13 143 and is highly active against most strains of *S. aureus* [14]. Cross-resistance with other antibiotic
14
15 144 groups is very uncommon. Nevertheless, because of the risk of the development of resistance
16
17 145 when administered as monotherapy, fosfomycin must be administered in combination with
18
19 146 another antibiotic [15]. *In vitro* and small scale studies have demonstrated a synergistic effect
20
21 147 of cloxacillin plus fosfomycin against *S. aureus* [16], and several different beta-lactam
22
23 148 combinations have been successfully used in difficult-to-treat methicillin-resistant *S. aureus*
24
25 149 (MRSA) infections [17][18].

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30 150 In a recent multicentre trial, we showed that daptomycin plus fosfomycin in MRSA
31
32 151 bacteraemia achieved better outcomes in a subgroup of younger severely ill patients and
33
34 152 faster clearance of bacteraemia than daptomycin alone [19]. To date, however, no other
35
36 153 randomised studies evaluating the efficacy of cloxacillin plus fosfomycin for treating MSSA
37
38 154 bacteraemia have been published or registered in the ClinicalTrials.gov database.

39
40
41 155 We hypothesize that combining cloxacillin plus fosfomycin during the initial seven days of
42
43 156 treatment achieves better outcomes than cloxacillin alone in patients with MSSA bacteraemia.
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45 157 The primary objective of the study is to determine and compare mortality, clinical and
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47 158 microbiological failure at 7 and 90 days after randomisation by allocated treatment.

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162 **Methods and analysis**

163 **Study design and setting**

164 We will perform a multicentre, superiority, randomised, open-label, phase IV-III, two-armed
165 parallel group (1:1) clinical trial. Patients will be recruited from 20 tertiary hospitals in Spain (a
166 list of study sites is available in the Supplementary material). The trial has been registered in
167 the EudraCT and ClinicalTrials databases. The protocol follows the Standard Protocol Items:
168 Recommendations for Interventional Trials (SPIRIT) initiatives, and the results will be
169 presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT)
170 statement[20] [21].

171

172 **Study population**

173 *Inclusion criteria:*

- 174 - Subjects aged ≥ 18 years;
- 175 - At least one blood culture positive for MSSA ≤ 72 hours before inclusion, with evidence of
176 active infection;
- 177 - Written informed consent from the participant or the legal representative.

178

179 *Exclusion criteria:*

- 180 - Severe clinical status with expected death < 24 h.
- 181 - Severe hepatic cirrhosis (Child-Pugh C).
- 182 - Moderate-severe cardiac chronic failure (NYHA III-IV).
- 183 - Prosthetic endocarditis.
- 184 - History of significant allergy to β -lactams or fosfomycin (defined as previous type 1
185 hypersensitivity reaction to any β -lactams or fosfomycin, or history of serious non-type 1
186 hypersensitivity reaction to any penicillin or fosfomycin).
- 187 - Known *S. aureus* fosfomycin non-susceptibility.

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3 188 - Polymicrobial bacteraemia with more than one microorganism in blood cultures.
4
5 189 - A positive pregnancy test or pregnancy or lactation at the time of inclusion.
6
7 190 - Myasthenia gravis.
8
9 191 - Participation in another clinical trial.
10
11
12 192 - Previous participation in the present clinical trial.
13
14 193 - Social problems, cognitive or psychiatric impairment which might be expected to affect
15
16 194 adherence to the protocol.
17
18 195 - Acute SARS-CoV2 infection.
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22
23 **197 Intervention**

24
25 198 Patients will be randomly assigned to receive intravenous cloxacillin 2g every four hours plus
26
27 199 fosfomycin 3 g every six hours, or to receive cloxacillin 2 g every four hours intravenously for
28
29 200 the duration of seven days. If creatinine clearance is <30 mL/min, cloxacillin will be
30
31 201 administered at dose of 2g every six hours. The fosfomycin dose will be adjusted according to
32
33 202 creatinine clearance, as explained in Table 1.

34
35 203 This treatment will be administered during the first seven days after randomisation. After the
36
37 204 first week, the choice of antibiotic strategy and the duration of overall antibiotic treatment will
38
39 205 be determined according to clinical criteria by the attending physician, based on current
40
41 206 guidelines. Uncomplicated bacteraemia (no evidence of complicated bacteraemia) will be
42
43 207 treated for 10-14 days, and complicated bacteraemia (defined as infection with hematogenous
44
45 208 seeding, progression of infection beyond the primary focus, persistent bacteraemia, skin
46
47 209 alterations suggestive of acute systemic infection, presence of noncatheter device,
48
49 210 haemodialysis) for 4-6 weeks at least, depending on the source of the infection and other
50
51 211 clinical considerations [22][23]. Removal of a focus of infection as soon as possible and
52
53 212 performance of echocardiogram will be prioritised. The assessment schedule is summarised in
54
55 213 Table 2. A schematic diagram of study design is shown in Figure 1.
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5 215 **Outcomes**

6
7 216 Efficacy will be analysed by intention to treat in all randomised patients, using a hierarchical
8
9 217 testing procedure in the following order: treatment success at day 7 followed by treatment
10
11
12 218 success at TOC visit. Furthermore, a per-protocol analysis will also be performed.

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16 220 **Primary endpoints:**

17
18 221 Treatment success at day 7 from randomization is a composite outcome defined by all the
19
20
21 222 following criteria met after randomisation:

- 22
23 223 - Patient alive at day 7 AND
24
25 224 - Clinical improvement measured by stable or improved quick SOFA score (compared
26
27 225 with baseline) at day 7 AND
28
29 226 - Patient afebrile at day 7 AND
30
31
32 227 - Negative MSSA blood cultures at day 7.

33
34 228 Treatment success at TOC visit, defined by presence of all of the following:

- 35
36 229 - Patient alive at TOC;
37
38
39 230 - No isolation of MSSA in blood culture and/or at another sterile site from day 8 until
40
41 231 the TOC visit (12 weeks after randomisation). In case of patients with a prolonged
42
43 232 course of antibiotic treatment (more than 10 weeks), the TOC visit will be performed
44
45 233 two weeks after the end of treatment (EOT).

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49
50 235 Treatment failure is defined by the presence of one of the following conditions: all-cause
51
52 236 mortality at TOC, withdrawal from the study due to adverse events related to the treatment,
53
54 237 requirement of an additional MSSA-active antibiotic until day 7, and lack of clinical
55
56 238 improvement at day 7.

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3 240 **Secondary endpoints**
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5 241 *Clinical:*
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- 7 242 - All-cause mortality at day 7, EOT and TOC visit.
8
9 243 - Persistent bacteraemia (at least one positive blood culture) at day 3 and persistent
10
11 244 bacteraemia at day 7 after randomisation.
12
13 245 - Microbiological relapse, defined by at least one positive blood culture for MSSA at
14
15 246 least 72 hours after a preceding negative culture.
16
17 247 - Microbiological treatment failure, defined by a positive sterile site culture for MSSA at
18
19 248 least 14 days after randomisation.
20
21 249 - Number of patients with persistent and relapsing bacteraemia.
22
23 250 - Number of patients with complicated bacteraemia, defined as persistent bacteraemia,
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25 251 endocarditis or metastatic emboli, presence of prosthetic devices.
26
27 252 - Length of intensive care unit stay.
28
29 253 - Duration of intravenous antibiotic treatment.
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34 254 We will perform exploratory subgroup analyses for patients at high risk (those with metastatic
35
36 255 infection, unknown focus of bacteremia, endocarditis, and pneumonia) for both primary
37
38 256 outcomes. On participants with persistent bacteremia subgroup analysis will be focused on
39
40 257 treatment success at TOC.
41
42

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45 259 *Microbiological:*
46

- 47 260 - *In vitro* cloxacillin plus fosfomicin combination synergy (see Supplementary material).
48
49 261 - Emergence of fosfomicin-resistant strains during therapy in the combination
50
51 262 treatment arm.
52
53 263 - Operon *agr* functionality and its relationship with Minimum Inhibitory Concentration
54
55 264 (MIC) changes to vancomycin (VAN) and daptomycin (DAP) and with biofilm
56
57 265 production.
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3 266 - VAN and DAP MIC as markers of complications during bacteraemia. Isolates with rising
4
5 267 vancomycin MICs are associated with thicker cell walls and dysfunctional *agr* profiles.
6
7 268 These profiles are involved in quorum sensing, activation of *S. aureus* toxins and other
8
9 269 virulence factors, leading to more resistant but less virulent strains.
10
11
12 270 - Whole genome sequencing and its changes in patients with treatment failure.
13
14 271

15
16 272 *Pharmacological:*

17
18 273 Patients recruited at the coordinating centre (Bellvitge University Hospital) will be included in a
19
20 274 pharmacological sub-study, after obtaining additional signed informed consent. The variables
21
22 275 assessed will be:

- 23
24
25 276 - Minimum and maximum concentration in steady state of fosfomycin and cloxacillin,
26
27 277 and pharmacokinetic variability of these concentrations.
28
29 278 - Associations between pharmacokinetic parameters and efficacy.
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34 280 *Safety:*

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36 281 Safety of cloxacillin plus fosfomycin as compared with cloxacillin alone (See Supplementary
37
38 282 material).
39

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43 284 **Follow-up and data collection**

44
45 285 During the first week of treatment, all patients will be assessed at days 1, 3 and 7 by a member
46
47 286 of the investigating team, and followed up daily by an infectious diseases specialist. Scheduled
48
49 287 visits are reported in Table 2. A follow-up visit will be arranged for all participants at EOT (48h
50
51 288 after the last dose of antibiotic treatment) and at TOC. At this last visit, a structured telephone
52
53 289 interview will be performed to assess outcomes.
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3 290 All data will be recorded on a secure web application used for building and managing online
4
5 291 databases (REDCap). Authorised staff will be free to examine the records for quality assurance
6
7 292 and audit purposes.
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11 294 **Endpoint assessment**

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13
14 295 The primary endpoints will be assessed by a committee comprising three independent senior
15
16 296 infectious disease specialists with extensive experience in *S. aureus* bacteraemia and
17
18 297 endocarditis. This committee will be blinded to treatment allocation and to patient
19
20 298 identification. Committee members will receive a data extract containing patients'
21
22 299 demographical data, comorbidities, source of infection, quick SOFA score at baseline and day
23
24 300 7, date and results of blood and sterile cultures between randomisation and TOC, as well as
25
26 301 date of death if applicable.
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31 303 **Statistical analysis plan**

32 304 *Sample size*

33
34
35 305 Prior data indicate a success rate in the cloxacillin alone group of 74% [4]. To achieve a success
36
37 306 rate in the experimental group of 86% (i.e., an absolute difference of 12%, considered as
38
39 307 clinically significant) we will need 183 experimental subjects and 183 control subjects to reject
40
41 308 the null hypothesis of an equal success rate with a probability of 80%. The probability of type I
42
43 309 error associated with this test is 5%, and a drop-out rate of 5% has been anticipated.
44
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48 310 *Allocation*

49
50 311 Participants will be block randomised to receive monotherapy or combination using an
51
52 312 internet-based, concealed computer-generated random allocation sequence. Random blocks
53
54 313 will be of size 4 or 6. The randomised sequence allocation will be stored in the Biostatistics
55
56 314 Unit at Biomedical Research Institute of Bellvitge (IDIBELL) and will not be available to any
57
58 315 member of the research team.
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3 316 *Data analysis*
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5 317 The main analysis will be performed for the intention to treat population, which will include all
6
7 318 randomised patients included in the study with a primary outcome assessment. If no statistical
8
9 319 significance is detected by day 7 in the hierarchy, then no further hypothesis testing will be
10
11 320 performed. The analysis will be repeated in the per protocol population. All patients who
12
13 321 receive at least one dose of treatment will be included in the safety analysis.
14
15

16 322 The Chi-square test will be used to test the binary endpoints of the success rate. The relative
17
18 323 risk for success rate will be calculated, accompanied by 95% confidence intervals. Absolute risk
19
20 324 difference and 95% confidence interval will also be reported. The time-to-event outcomes,
21
22 325 including the time of response, and overall survival will be estimated using the Kaplan-Meier
23
24 326 method [24]. To account for competing risks, cause-specific cox regression models will be
25
26 327 used, and event cause cumulative incidence functions will be plotted [25]. All analyses and
27
28 328 data management will be performed with R software, version 4.0.4 or superior [26].
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34 330 **Monitoring**

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36 331 *Monitoring plans*
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39 332 The data monitoring board will ensure the correct progress of the study in terms of safety, and
40
41 333 also the sample size assumptions.
42

43 334 *Harms - Data Safety and Monitoring Board (DSMB)*
44

45 335 An independent DSMB will review safety data and provide advice about the continuation,
46
47 336 modification and/or termination of the study, as well as adherence to the protocol,
48
49 337 recruitment, outcomes and additional data related to participants' safety. The DSMB will be
50
51 338 composed by specialists in pharmacology, biostatistics and infectious diseases. The review by
52
53 339 the DSMB will be performed when half of the sample size will be reached.
54
55

56 340 *Adverse events reporting and quantification*
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3 341 An adverse event will be defined as any injury related to medical management occurring
4
5 342 during the patient's participation in the study, even if it is not related to the study medication.

6
7 343 An adverse drug event will be defined as any medication-related adverse event occurring
8
9 344 during the patient's participation in the clinical trial.

10
11
12 345 An adverse drug reaction will be defined as any 'adverse drug event' occurring when the
13
14 346 medication is used as directed and at the usual dosage.

15
16 347 Serious adverse event or reaction will be defined as an event or reaction that:

- 17
18 348 - Results in death;
19
20 349 - Is life-threatening;
21
22
23 350 - Causes persistent or significant disability;
24
25 351 - Causes a congenital anomaly/birth defect;
26
27
28 352 - Requires in-patient hospitalisation or prolongation of existing hospitalisation (not
29
30 353 related to basal diseases).

31
32 354 *Adverse drug events of particular interest for the study*

33
34 355 - Hypokalaemia and hypocalcaemia: blood analysis will be performed every 2-3 days
35
36 356 during the first week to permit potassium and calcium control. Furthermore,
37
38 357 administration of potassium supplement will be recommended from the first day of
39
40 358 treatment to avoid this complication.

41
42
43 359 - Sodium overload: since both fosfomycin and cloxacillin carry a high sodium load, daily
44
45 360 physical examination and administration of a low dose of a diuretic such as furosemide
46
47 361 will be recommended to avoid hypertension, oedema and acute cardiac failure.

48
49
50 362 *Reporting*

51
52 363 Any adverse events occurring during the patient's participation in the clinical trial will be
53
54 364 recorded on the clinical chart by the principal investigator at each scheduled visit. The principal
55
56 365 investigator will record its possible relationship to the study drug.
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3 366 The electronic case report form should record only the following: serious adverse drug events;
4
5 367 adverse events (of any degree) related to the study medication, in the opinion of the PI;
6
7 368 adverse events (of any degree) leading to modification of the dosage of the study drug or its
8
9
10 369 interruption/early discontinuation; adverse events of particular interest for the study.

11
12 370 The sponsor will be notified of all serious adverse events within 24 h of their occurrence.
13
14 371

15
16 372 **Trial status**

17
18 373 The SAFO trial opened its first recruitment site on 31 May 2019. The first patient was enrolled
19
20 374 on 1 July 2019. Follow up is expected to be completed by May 2022.
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24
25 376 **Declaration**

26
27 377 *Ethics*

28
29 378 The trial will be conducted in accordance with the principles of the most recent Declaration of
30
31 379 Helsinki (agreed by the 64th World Medical Association General Assembly in 2013), the Good
32
33 380 Clinical Practice (GCP) guidelines, and the current local legislation.

34
35 381 The study was authorised by the Spanish Medicines and Healthcare Products Regulatory
36
37 382 Agency (AEMPS, 18-0905) and by the Bellvitge University Hospital Ethics committee
38
39 383 (AC069/18).

40
41 384 The principal investigator or collaborator at each site will provide patients with the information
42
43 385 sheet, and s/he will explain the nature of the study and the objectives and clarify any doubts.

44
45 386 Written informed consent will be obtained from all patients or from their legal representatives
46
47 387 (LRs) if they lack capacity, before enrolment (Supplementary file). Patients (or their LR) are
48
49 388 free to withdraw from the trial at any time; this will be explicitly stated on the patient's
50
51 389 information sheet.

52
53 390 Patients' personal and clinical information will be managed in accordance with European
54
55 391 Regulation 2016/679 and Spanish legislation. The trial protocol was approved by the research
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3 392 ethics committee on 28 March 2019 and by the AEMPS on 8 April 2019. The informed consent
4
5 393 form and information sheet were approved by the research ethics committee on 28 March
6
7 394 2019. The emendation regarding “acude SARS-CoV2 infection” as exclusion criteria was
8
9 395 approved by the research ethics committee and by the AEMPS on 29 November 2020.

11
12 396 *Data sharing plan and dissemination*

13
14 397 Sharing of data generated by this project is an essential part of our proposed activities and will
15
16 398 be carried out in several different ways. We would wish to make our results available both to
17
18 399 the community of scientists interested in infectious diseases and the biology of *Staphylococcus*
19
20 400 *aureus* to avoid unintentional duplication of research.

21
22
23 401 The preliminary results will be presented at international and national infectious diseases
24
25 402 conferences and will be published in peer-reviewed journals. The results will also be made
26
27 403 available to patients, caregivers and funders through press and social media communications.

28
29 404 A corporative *Twitter* account will be created to establish direct contact with the general
30
31 405 public and other health-care professionals. Any formal presentation or publication of data
32
33 406 collected from this study will be considered as a joint publication by the participating
34
35 407 investigators and will follow the recommendations of the International Committee of Medical
36
37 408 Journal Editors (ICMJE).

38
39 409 Individual participant data that underlie the results, after deidentification (text, tables, figures,
40
41 410 and appendices) will be available immediately following publication and ending 5 years
42
43 411 following article publication. Data will be shared with researchers who provide a
44
45 412 methodologically sound proposal to achieve aims in the approved suggestions. Propositions
46
47 413 should be directed to the corresponding author.

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49
50 414 *Patients and public involvement*

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52 415 Patients will not be involved in either the enrolment or the execution of the trial, or in the
53
54 416 assessment of the interventions. However, before the beginning of the study, a number of
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3 417 patients with previous *S. aureus* bacteraemia were contacted by phone to obtain their
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5 418 feedback about the study.
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10 420 **Protocol amendments**

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12 421 No protocol modifications will become effective until approved by the relevant authorities and
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14 422 by the Drug Research Ethics Committee (CEIm). Exceptions will be made for any changes to
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16 423 protect patients from imminent harm and those concerning exclusively logistic or
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18 424 administrative aspects.
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3 507 *Authors' contributions*
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6 508 SG, GC, JM, JC, DB, MD, AP, SC and MP conceived and designed the study. SG, GC, MP and JC
7
8 509 wrote and revised the manuscript. CT and NP designed and wrote statistical analysis plan. PH
9
10 510 and SV critically reviewed the protocol. SG, GC, RSJ, JA, LM, SGZ, JLC, OG, AGG, SI, GGP, EC,
11
12 511 LBP, IO, AJS, LELC, GE, MA, MJGP, FG, JRP, MLPB, RB, MTPR, YM, MBLV and GH will contribute
13
14 512 to the acquisition of data. All authors have read and approved the final manuscript.
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18 513 *Trial sponsor:* Miquel Pujol, MD PhD. Department of Infectious Diseases, Hospital Universitari
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20 514 de Bellvitge, Institut Investigacions Biomèdiques de Bellvitge (IDIBELL), Carrer de la Feixa
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22 515 Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona. Tel.: +34. 93 2602487
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26 516 *Funding statement*
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30
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35 520 2021 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de
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39 522 Network for Research in Infectious Diseases (REIPI RD16/0016/0005).
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47
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49
50 526 for technical help.
51

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53 527 *Competing interests*
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56 528 GH received a research grant from ERN (19PNJ145).
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60 529 *List of abbreviation*

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3 530 MSSA: Methicillin-susceptible *Staphylococcus aureus* bacteraemia. TOC: test of cure. SPIRIT:
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5 531 Standard Protocol Items: Recommendation for Interventional Trials. CONSORT: Consolidated
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7 532 Standards of Reporting Trials. SOFA: Sequential Organ Failure Assessment. MRSA: Methicillin-
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9 533 resistant *Staphylococcus aureus*. EOT: End of Treatment. GCP: Good Clinical Practice.
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534 **Tables**535 **Table 1.** Fosfomycin dosage adjusted to renal function.

Creatinine clearance (mL/min)	Fosfomycin dosage
>40	3 g every 6 hours
20-40	3 g every 12 hours
10-20	3g every 24 hours
<10	3 g every 48 hours
Haemodialysis	3 g after haemodialysis
Continuous renal replacement therapy	3 g every 24 hours

536 Abbreviations: mL: millilitre; min: minute.

537 **Table 2.** The SAFO evaluation schedule.

	Visit				Unscheduled			
	Day	Screening	0	3	7	EOT	Visit ¹	TOC
All patients								
Eligibility criteria		X						
Pregnancy test ²		X						
Informed consent		X						
Randomisation			X					
Clinical evaluation			X	X	X	X	X	X ³
Quick SOFA score			X		X			
Blood cultures			X	X	X	X	X	X ³
Blood count and biochemical analysis ⁴			X	X	X		X	X ³
Adverse events record				X	X	X	X	X
Concomitant medication			X	X	X	X		
Subgroup of patients with PK/PD sub analysis								
Lithium heparin blood sample (2x 5mL)					X			

538 ¹Unscheduled visit will be performed only in case of clinical infectious symptoms and signs.

539 ²Pregnancy test will be performed only in woman of childbearing age.

540 ³In absence of infective symptoms, clinical assessment may be made by phone call; blood culture and
541 blood analysis will not be necessary.

542 ⁴Complete blood count, biochemical analysis (C-reactive protein-, creatinine, urea, creatinine clearance,
543 AST, ALT, bilirubin, sodium, potassium, calcium, acid-base analysis) and coagulation test (prothrombin
544 test/INR).

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545 **Figures**

546 **Figure 1.** Study design.

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550 **Supplementary material**

551 **List of study sites:** Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona;
552 Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona;
553 Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona;
554 Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mútua de Terrassa,
555 Barcelona; Corporació Sanitaria Parc Taulí, Sabadell, Barcelona; Hospital Universitari Sant Joan,
556 Reus; Hospital Universitario M.Broggi, Sant Joan Despí, Barcelona; Hospital Universitario 12 de
557 Octubre, Madrid; Hospital Universitario Virgen Macarena, Seville; Hospital Universitario de
558 Cruces, Barakaldo; Hospital Universitario Lucus Augusti, Lugo; Hospital Clínico Universitario de
559 Zaragoza, Zaragoza; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitari
560 Germans Trias, Badalona; Hospital Universitario Álvaro Cunqueiro, Vigo; Hospital de Barcelona,
561 Barcelona; Hospital Universitario La Paz, Madrid.

562 Other hospitals may be added during the course of the clinical trial.

563

564 **Microbiological studies**

565 In fosfomicin resistant SASM strains, synergy studies between cloxacillin and fosfomicin will be
566 assessed by E-test and time-kill assays.

567 For the time-kill assays 0.25, 0.5 and 1 fold MIC for each antibiotic will be tested. Synergy for
568 the combination is defined as $>2 \log_{10}$ CFU/mL decrease in comparison with that by the most
569 active antibiotic of the combination tested, and antagonism is defined as $>2 \log_{10}$ CFU/mL
570 increase.

571 For the E-test, we calculate the fractional inhibitory concentration index (FICI) with the
572 following formula: $FICI = (MICCF/MICC) + (MICBFC/MICF)$, where MICCF is the MIC of cloxacillin
573 tested in combination with fosfomicin, MICC and MICF are the MIC of cloxacillin and
574 fosfomicin tested alone, MICFC is the MIC of fosfomicin tested in combination with cloxacillin.

575 Synergy is defined as a FICI ≤ 0.5 , indifference as a FICI between >0.5 and 4 and antagonism as a

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8 578 **Safety outcomes**
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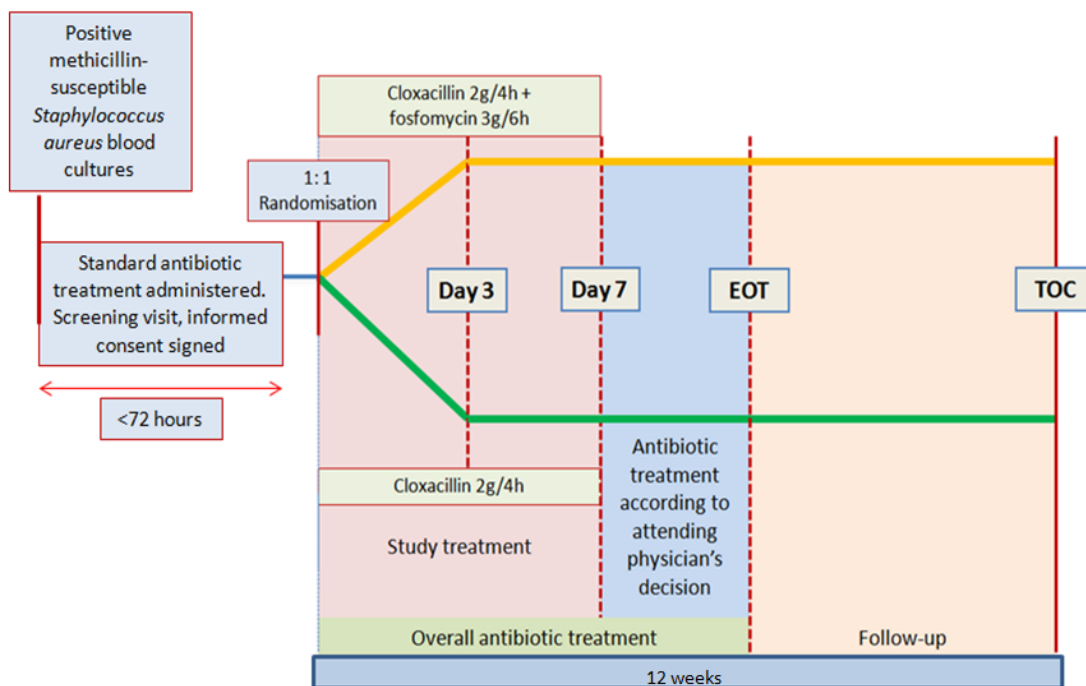
10 579 We will compare incidence of serious adverse events (SAEs) in both group. Particularly, we will
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12 580 assess the incidence of acute cardiac failure, hypokalemia, hypocalcemia, methabolic alkalosis
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14 581 and hypernatremia.
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18 583 Additional ethical information
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21 584 Patients' data will be anonymised; each patient will be identified by a code. Only the study
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23 585 physician and collaborators will have access to patients' clinical histories. Consequently,
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25 586 patients' identities will not be revealed to any other person, except in cases of medical
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27 587 emergency or if required by law. Access to patient information will be restricted to the study
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29 588 physician and collaborators, the health authorities (AEMPS), the Clinical Research Ethics
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31 589 Committee, and personnel authorised by the sponsor when they need to check the data and
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33 590 procedures used in the study, but always maintaining the confidentiality of the information in
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35 591 accordance with the current legislation.
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1 **Supplementary material**

2 **List of study sites:** Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona;
3 Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona;
4 Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona;
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7 Reus; Hospital Universitario M.Broggi, Sant Joan Despí, Barcelona; Hospital Universitario 12 de
8 Octubre, Madrid; Hospital Universitario Virgen Macarena, Seville; Hospital Universitario de
9 Cruces, Barakaldo; Hospital Universitario Lucus Augusti, Lugo; Hospital Clínico Universitario de
10 Zaragoza, Zaragoza; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitari
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12 Barcelona; Hospital Universitario La Paz, Madrid.
13 Other hospitals may be added during the course of the clinical trial.

15 **Microbiological studies**

16 In fosfomicin resistant SASM strains, synergy studies between cloxacilin and fosfomicin will be
17 assessed by E-test and time-kill assays.

18 For the time-kill assays 0.25, 0.5 and 1 fold MIC for each antibiotic will be tested. Synergy for
19 the combination is defined as $>2 \log_{10}$ CFU/mL decrease in comparison with that by the most
20 active antibiotic of the combination tested, and antagonism is defined as $>2 \log_{10}$ CFU/mL
21 increase.

22 For the E-test, we calculate the fractional inhibitory concentration index (FICI) with the
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24 tested in combination with fosfomicin, MICC and MICF are the MIC of cloxacillin and
25 fosfomicin tested alone, MICFC is the MIC of fosfomicin tested in combination with cloxacillin.
26 Synergy is defined as a FICI ≤ 0.5 , indifference as a FICI between >0.5 and 4 and antagonism as a

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8 29 **Safety outcomes**
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10 30 We will compare incidence of serious adverse events (SAEs) in both group. Particularly, we will
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12 31 assess the incidence of acute cardiac failure, hypokalemia, hypocalcemia, metabolic alkalosis
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18 34 Additional ethical information
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22 36 physician and collaborators will have access to patients' clinical histories. Consequently,
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HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

EudraCT num.: 2018-001207-37

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge

Investigador principal:

Centro:

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por el Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir.

Además, puede consultar con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria.

OBJETIVO DEL ESTUDIO

La bacteriemia por *Staphylococcus aureus*, que es la enfermedad que usted padece ahora, es una infección muy frecuente y que presenta una elevada mortalidad. El tratamiento actual es la Cloxacilina como único fármaco.

El objetivo es establecer si añadir otro antibiótico (Fosfomicina) al tratamiento habitual con Cloxacilina mejora el pronóstico de esta infección.

HOJA DE INFORMACIÓN AL PACIENTE

DESCRIPCIÓN DEL ESTUDIO

El presente estudio prevé la inclusión de 366 pacientes y se realizará en 15 diferentes hospitales en toda España.

Tanto la Cloxacilina como la Fosfomicina son fármacos que ya están comercializados y se utilizan en la práctica clínica habitual.

El estudio pretende que algunos pacientes además de recibir el tratamiento con cloxacilina (que es el tratamiento habitual de esta infección) reciban también otro antibiótico asociado, la fosfomicina. La combinación de estos dos antibióticos pretende mejorar el control de la infección y así disminuir las complicaciones que esta infección comporta.

Los pacientes recibirán el tratamiento de estudio o el tratamiento habitual. El que Usted reciba el tratamiento de estudio (Cloxacilina + Fosfomicina) o el tratamiento habitual (Cloxacilina sola) será determinado por el azar a través de una asignación por un programa informático. Usted tiene la misma probabilidad que le toque uno u otro tratamiento.

Por el diseño del estudio, tanto su médico habitual como usted sabrán en todo momento que medicación está recibiendo. La medicación será administrada por vía intravenosa.

ACTIVIDADES DEL ESTUDIO

El tratamiento de estudio durará 7 días, después de los cuales el tipo de tratamiento y la duración serán decididos por su médico habitual según la práctica clínica habitual. El seguimiento será de 12 semanas después del comienzo del tratamiento.

Si acepta participar en el estudio, además de las visitas que realizará su equipo médico habitual, se le realizarán 5 visitas extras (el primero, tercero y séptimo día de tratamiento, al final del tratamiento total y después de 12 semanas desde el comienzo del tratamiento). En caso que usted lo necesite (si presentara fiebre por ejemplo) se le realizará una visita extra entre la visita 4 y la visita 5.

Durante las visitas de la 1 a la 5, y en la visita extra si lo requiriese, el equipo investigador realizará una evaluación clínica que incluirá ver si tiene fiebre, conocer su tensión arterial y exploración física general. Comprobará también los resultados de análisis de sangre (hemograma, función renal y hepática, iones y equilibrio ácido-base venoso) que le haya realizado su equipo médico ese día.

También durante todas las visitas se solicitarán 2 muestras de sangre de 10 mL (hemocultivos) para asegurar que la bacteria que le ha producido la enfermedad ha desaparecido de su sangre.

Durante el estudio no se le realizarán analíticas complementarias a las que se realizan en la práctica habitual de su enfermedad.

Las muestras obtenidas se utilizaran para los análisis del estudio, pero no se prevé su almacenamiento una vez concluidos los análisis del estudio.

HOJA DE INFORMACIÓN AL PACIENTE Visita 1	Visita 2	Visita 3	Visita 4	Visita 5
Día de la inclusión	Día +3 desde inicio tratamiento del estudio	Día + 7 desde inicio tratamiento del estudio	A las 48 h de la finalización del ciclo de tratamiento antibiótico completo	+ 12 semanas de la asignación aleatoria
Exploración física	Exploración física	Exploración física	Exploración física	Exploración física
Test de embarazo				
Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)	Obtención de muestra de sangre (10 mL)
En caso de fiebre o síntomas de infección entre la visita 4 y la visita 5, se realizará una visita extraordinaria donde se le realizará una exploración física y se obtendrán muestras de sangre.				

RIESGOS Y MOLESTIAS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Los fármacos utilizados en este estudio están autorizados para el tratamiento de la enfermedad que Usted padece. Están comercializados desde hace muchos años y se utilizan en la práctica clínica habitual.

Los efectos secundarios principales que pueden presentarse con ambos fármacos son la sobrecarga de sodio y la posibilidad de un descenso del potasio. La sobrecarga de sodio, podría desencadenar episodios de insuficiencia cardíaca y será valorada en las visitas y se administrará tratamiento diurético cuando sea necesario. La hipokalemia (descenso del potasio en sangre), se puede corregir con la administración de potasio a través de sueros o por vía oral. Ambas eventualidades serán valoradas y se realizarán controles y medidas para evitar su desarrollo. Otros efectos secundarios descritos con la fosfomicina son: reacciones cutáneas por hipersensibilidad, aumento transitorio de los enzimas hepáticos, náuseas, diarreas, hipocalcemia (descenso de calcio en sangre) y alcalosis metabólica.

Al ser, tanto la cloxacilina como la fosfomicina, fármacos aprobados por las autoridades sanitarias competentes, existe información al acceso de todo el mundo sobre los efectos secundarios. Por favor, hable con el médico de su estudio para obtener una lista completa de los efectos secundarios comunicados con este fármaco y en cualquier caso se le entregará el prospecto del fármaco.

Si acepta participar al estudio, acepta acudir a las visitas de seguimiento y de notificar cualquier evento adverso que le suceda o cambios en medicación, advirtiéndole que, excepto en caso de urgencia, no modifique la medicación que está tomando ni tome otros medicamentos o "plantas medicinales" sin consultar antes con el médico del estudio.

HOJA DE INFORMACIÓN AL PACIENTE

Todos los procedimientos que se realizarán durante el ensayo clínico son procedimientos habituales de la práctica clínica. La participación al ensayo supone la extracción de muestras de sangre (hemocultivos) en diferentes momentos, que no difiere de la práctica clínica habitual. Este procedimiento, aunque de bajo riesgo, en ocasiones puede producir hemorragias, hematomas, molestias, infecciones y/o dolor en el punto de extracción de sangre. También puede sentirse mareado.

Los posibles riesgos derivados del procedimiento realizado para la obtención de estas muestras estarán cubiertos por la póliza del seguro del centro hospitalario.

La realización de pruebas diagnósticas (pruebas de imagen o de obtención de muestras clínicas) o terapéuticas invasivas (drenaje de material purulento, desbridamiento quirúrgico), se realizarán según la práctica clínica habitual. La participación al presente ensayo no supone realizar más pruebas de las necesarias.

POSIBLES BENEFICIOS

El posible beneficio de su participación en el estudio es la mejora del tratamiento de la patología en los futuros pacientes. De todas maneras, es posible que no obtenga ningún beneficio para su salud por participar en este estudio.

ADVERTENCIA RELATIVA AL EMBARAZO

Se realizará un test de embarazo antes del comienzo del estudio en las mujeres en edad fértil. Los fármacos empleados en este estudio deben evitarse durante el embarazo. No hay literatura que haya demostrado toxicidad fetal en caso de uso de Cloxacilina. Para lo que concierne la Fosfomicina, se ha demostrado toxicidad para el feto en animales sólo a dosis que provocarían toxicidad materna.

En caso de producirse un embarazo durante su participación en el estudio debe informar a su médico de inmediato para recibir la asistencia médica adecuada. Se solicitará el consentimiento de la recogida de datos del mismo y de datos de salud del bebé hasta 3 meses después (Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales).

TRATAMIENTOS ALTERNATIVOS

No existen actualmente tratamientos alternativos que hayan demostrado la superioridad respecto al tratamiento habitual con Cloxacilina. Dada la elevada mortalidad de la enfermedad, en la práctica clínica habitual se utilizan diferentes combinaciones de tratamiento, sin que éstas hayan demostrado ser más eficaces que el tratamiento de la cloxacilina sola. Si el paciente decide no participar en el estudio, podría recibir esta misma combinación u otro tratamiento.

HOJA DE INFORMACIÓN AL PACIENTE

SEGURO

Para la participación en este estudio Usted estará cubierto por la póliza de seguro de cada centro hospitalario. No está previsto contratar un seguro específico.

Le informamos que es posible que su participación en este ensayo clínico pueda modificar las condiciones generales y particulares (cobertura) de sus pólizas de seguros (vida, salud, accidente), por ello, le recomendamos que se ponga en contacto con su compañía de seguros y le informe de su participación en el mismo para determinar si podría afectar a su póliza de seguro actual o en el caso de que vaya a contratar una póliza nueva.

PROTECCIÓN DE DATOS PERSONALES

Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen al cumplimiento del Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD), así como al resto de leyes y normativa vigente y aplicable (Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales).

Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle (nombre ni apellidos, iniciales, dirección, nº de la seguridad social, etc), sino un código. El código que le identifica será asignado de manera aleatoria a través de un programa informático. Sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica.

Las muestras biológicas del estudio también estarán identificadas por su código asignado en el estudio acompañado del código de la visita, cumpliendo con lo expuesto en el párrafo anterior.

Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección (Agencia Española de Medicamentos y Productos Sanitarios, autoridades sanitarias extranjeras) y el personal autorizado por el Promotor (monitores, auditores), únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en esta ley.

De acuerdo a lo que establece la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio. Además también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador

Versión 4.0 del 10 de junio de 2020

HOJA DE INFORMACIÓN AL PACIENTE

principal del estudio o al Delegado de protección de datos de la institución, email: dataprotection@idibell.cat.

Si usted decide retirar el consentimiento para participar en este estudio, ningún nuevo dato será añadido a la base de datos, pero los datos que ya se hayan recogido hasta el momento no se podrán eliminar para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello y si así lo permite la ley y requisitos éticos aplicables.

Si se realizara una transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al/ a la Delegado de Protección de Datos del promotor [secretariaserveiiinfecciosos@bellvitgehospital.cat]

GASTOS Y COMPENSACIÓN

En caso de participar en este estudio, usted no tendrá ningún gasto adicional ocasionado por el estudio. No está prevista ninguna compensación económica por participar en el estudio.

OTRA INFORMACIÓN RELEVANTE

Una descripción de este ensayo clínico estará disponible en <http://reec.aemps.es>, según exige la legislación española. Cualquier nueva información referente a los fármacos utilizados en el estudio y que pueda afectar a su disposición para participar en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible.

Debe saber que puede ser excluido del estudio si el promotor o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca por la medicación en estudio o porque

consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio.

Al firmar la hoja de consentimiento adjunta, acepta cumplir con los procedimientos del estudio que se le han expuesto.

HOJA DE INFORMACIÓN AL PACIENTE

Debe usted saber que es posible que su médico de Atención Primaria tenga conocimiento de su participación en este estudio.

¿QUÉ TRATAMIENTO RECIBIRÉ CUANDO FINALICE EL ENSAYO CLÍNICO?

Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere el más adecuado para su enfermedad, pero es posible que no se le pueda seguir administrando la medicación del estudio. Por lo tanto, ni el investigador ni el promotor adquieren compromiso alguno de mantener dicho tratamiento fuera de este estudio.

CONTACTO EN CASO DE DUDAS

Si durante su participación tiene alguna duda o necesita obtener más información, póngase en contacto con Dr/a _____
y teléfono _____.

CONSENTIMIENTO INFORMADO

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus Cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge.

Investigador Principal:

Centro:

Yo (nombre y apellidos): _____

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: _____ (nombre del investigador)
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio cuando quiera, sin tener que dar explicaciones, sin que esto repercuta en mis cuidados médicos.
- Acepto que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.
Presto libremente mi conformidad para participar en el estudio.

Firma del participante
Fecha: ____/____/____
(Nombre, firma y fecha de puño y letra por el paciente)

Firma del investigador
Fecha: ____/____/____

Cuando se obtenga el CI en personas con capacidad modificada para dar su CI.

Firma del representante legal, familiar o
persona vinculada de hecho
Fecha: ____/____/____
(Nombre, firma y fecha de puño y letra por el representante)

Firma del investigador
Fecha: ____/____/____

CONSENTIMIENTO INFORMADO ORAL ANTE TESTIGOS

Título del estudio: “Ensayo clínico de fase IV-III, con asignación aleatoria, controlado, abierto y multicéntrico, con dos grupos paralelos, para evaluar la eficacia de la combinación de Cloxacilina y Fosfomicina versus Cloxacilina en monoterapia en el tratamiento de la bacteriemia por *Staphylococcus aureus* sensible a la Meticilina”

Código del estudio: HUB-IDIBELL-SAFO-4.3.1.

Promotor: Dr. Miquel Pujol i Rojo del Servicio de Enfermedades Infecciosas del Hospital Universitari de Bellvitge.

Investigador Principal:

Centro:

Yo, _____ (*nombre y apellidos del testigo*),
como testigo, afirmo que en mi presencia se ha informado a D/D^a
_____ (*nombre y apellidos del participante*) y se
ha leído la hoja de información que se le ha entregado sobre el estudio, de modo que:

- Ha podido hacer preguntas sobre el estudio.
- Ha recibido suficiente información sobre el estudio.
- Ha hablado con: _____ (*nombre del investigador*)
- Comprende que su participación es voluntaria.
- Comprende que puede retirarme del estudio cuando quiera, sin tener que dar explicaciones, sin que esto repercuta en sus cuidados médicos.
- Acepta que le comuniquen la información derivada de la investigación que pueda ser relevante para su salud.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Firma del testigo

Fecha: ____/____/____

(Nombre, fecha y firma de puño y letra por el paciente/testigo)

Firma del investigador

Fecha: ____/____/____

CONSENTIMIENTO INFORMADO ORAL ANTE TESTIGOS

El participante del estudio ha indicado que no puede leer /escribir.

Un miembro del personal del estudio le ha leído el documento de consentimiento, lo ha revisado y comentado con el participante y se le ha concedido la oportunidad de hacer preguntas o consultarlo con otras personas.

El testigo ha de ser una persona imparcial, ajena al estudio.

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

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	21
	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	12
	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)	12
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	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
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)	8

Methods: Participants, interventions, and outcomes

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	8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	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)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	10
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)	23
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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	13
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	13
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	12
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13				
14				
15		17b	If blinded, circumstances under which unblinding is permissible, and	NA
16			procedure for revealing a participant's allocated intervention during	
17			the trial	
18				
19				

Methods: Data collection, management, and analysis

20				
21				
22	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	12
23	methods		trial data, including any related processes to promote data quality (eg,	
24			duplicate measurements, training of assessors) and a description of	
25			study instruments (eg, questionnaires, laboratory tests) along with	
26			their reliability and validity, if known. Reference to where data	
27			collection forms can be found, if not in the protocol	
28				
29				
30		18b	Plans to promote participant retention and complete follow-up,	
31			including list of any outcome data to be collected for participants who	
32			discontinue or deviate from intervention protocols	
33				
34	Data	19	Plans for data entry, coding, security, and storage, including any	12
35	management		related processes to promote data quality (eg, double data entry;	
36			range checks for data values). Reference to where details of data	
37			management procedures can be found, if not in the protocol	
38				
39				
40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	13
41	methods		Reference to where other details of the statistical analysis plan can be	
42			found, if not in the protocol	
43				
44				
45		20b	Methods for any additional analyses (eg, subgroup and adjusted	12
46			analyses)	
47				
48		20c	Definition of analysis population relating to protocol non-adherence	13
49			(eg, as randomised analysis), and any statistical methods to handle	
50			missing data (eg, multiple imputation)	
51				

Methods: Monitoring

52				
53				
54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	14
55			and reporting structure; statement of whether it is independent from	
56			the sponsor and competing interests; and reference to where further	
57			details about its charter can be found, if not in the protocol.	
58			Alternatively, an explanation of why a DMC is not needed	
59				
60				

1				
2		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	14
3				
4				
5				
6	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	14
7				
8				
9				
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
12				
13				
14				
15				
16	Ethics and dissemination			
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
18				
19				
20	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)	17
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
27				
28				
29				
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
31				
32				
33	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
41				
42				
43				
44				
45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
49				
50				
51				
52				
53				
54		31b	Authorship eligibility guidelines and any intended use of professional writers	
55				
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
58				
59				
60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if 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](#)" license.

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