26es JNI 2025 TOURS
et la région Centre - Val de Loire VINCI
Journées Nationales d'infectiologie
du mercredi 11 juin 2025 au vendredi 13 juin 2025
Journée Nationale de Formation des Paramédicaux en Infectiologie
Jeudi 12 juin 2025

CloCeBa

Cloxacillin *versus* Cefazolin for methicillin-susceptible *Staphylococcus aureus* bacteraemia a randomised, controlled, non-inferiority trial

Charles Burdet, Nadia Saïdani, Céline Dupieux, Adrien Lemaignien, Etienne Canoui, Laure Surgers, Marina Esposito-Farèse, Vincent Le Moing, Pierre Tattevin, François Vandenesch, Xavier Duval, Sarah Tubiana, **François-Xavier Lescure** for the CloCeBa study group.

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ClinicalTrials.gov NCT03248063

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Déclaration de liens d'intérêt avec les industriels de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

L'orateur ne souhaite pas répondre ☐

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- **Titre** : CLOCEBA

• Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
• Conférencier ou auteur/rédacteur rémunéré d'articles ou documents		
• Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations	☐ OUI	☑ NON
• Investigateur principal d'une recherche ou d'une étude clinique	☑ OUI	☐ NON
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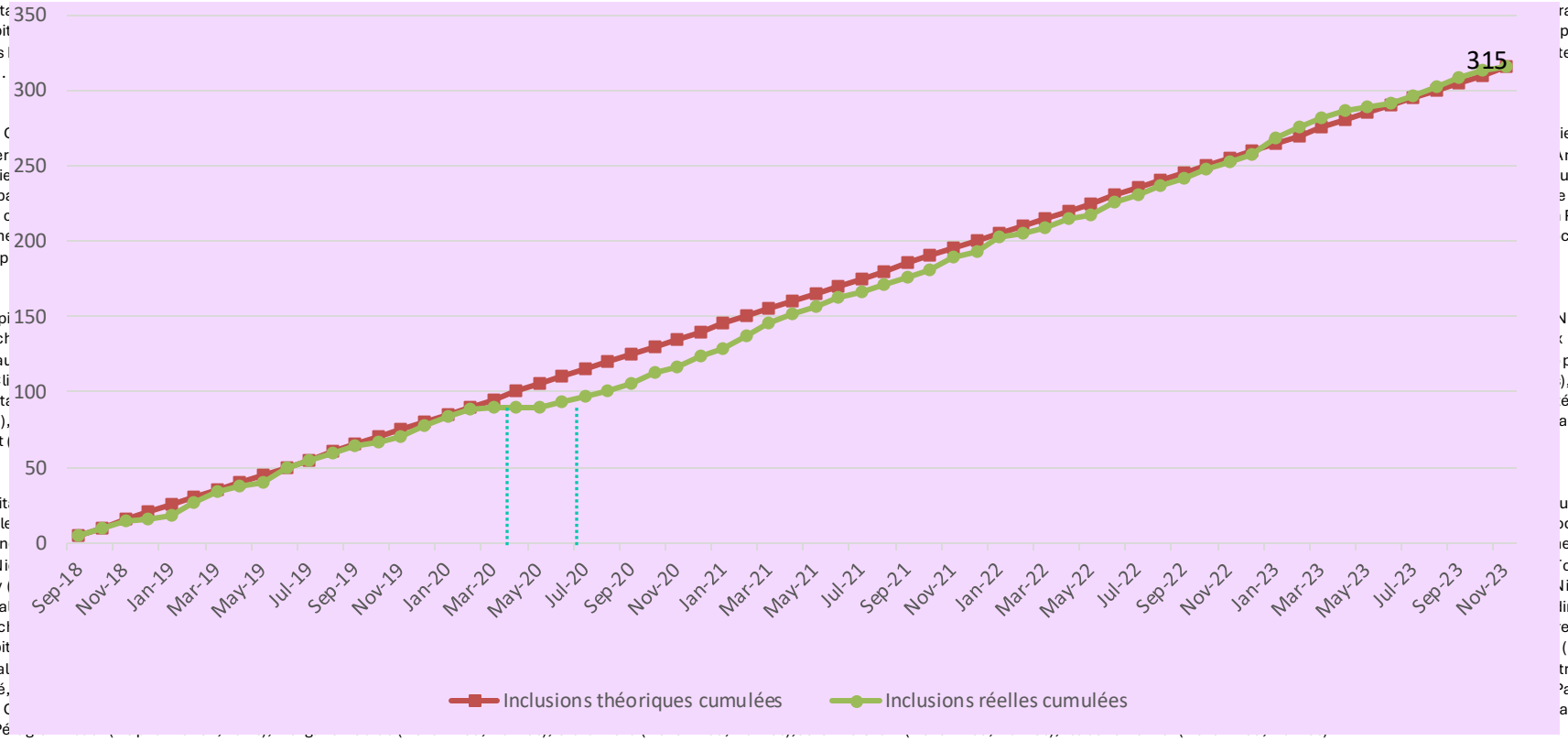

razia Tateo (Hôpital Saint Louis, Paris), Agathe Vigouroux (Hôpit pellier), Nathalie Pansu (Hopital Saint-Eloi, Montpellier), Lucas te (Hôtel Dieu, Nantes), Raphael Lecomte (Hôtel Dieu, Nantes).

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Introduction

- ***Staphylococcus aureus* bacteraemia (SAB)**
  - Annual incidence: 20-30 cases per 100 000 persons
  - Overall 3-month mortality rate around 25%

- **Antibiotic therapy**
  - Penicillin M : gold standard
  - Alternative options
    - ✓ Daptomycin non inferior but associated with resistant strain emergence
    - ✓ Glycopeptide
  - Adjunctive anti staph
    - ✓ have failed to prove their efficacy

- **Cloxacillin/Flucloxacillin**
  - Renal impairment in more than 10% of patients
  - Repeated shortages

→ Need for alternative therapy

Thorlacius-Ussing L. et al. Emerg Infect Dis 2019, Jokinen E et al. Infect Dis 2018, Bai et al. Clinical Microbiol and Infect 2022, Grillo S et al. Nature Med. 2023, Thwaites GE et al. Health Technol Assess 2018, Cheng MP et al. Clin Infect Dis 2021, Youngster I et al. Clin Infect Dis 2014

Introduction

- ***First-generation cephalosporins***
  - Have appeared as good candidates
  - Current use and recommendations as alternative agents in the treatment of MSSA-IE
  - Observational studies supported cefazolin use
    - ✓ No difference of efficacy
    - ✓ Better safety profiles
    - ⚠ biases

- ***Concerns***
  - No RCT assessed the efficacy of cefazolin in MSSA bloodstream infections
  - Impact of BlaZ genes in the case of high bacterial inoculum such as endocarditis or deep infection, raising the question of a reduced overall efficacy

Delgado V et al. European Heart J 2023, Loubet P et al. Clin Microbiol Infect 2018, Bourreau A. et al. Infect Dis Now 2023, Jean B et al. JAMA Ntew Open 2024

Design

- **Hypotheses**
  - Cefazolin has a **non-inferior efficacy** than cloxacillin for the treatment of MSSA bacteriemia
  - Cefazolin has a **better safety profile** than cloxacillin
- **Aim**
  - To compare, the efficacy, the safety and the ecological impact of cefazolin *vs* cloxacillin for the treatment of MSSA bacteremia in **adults**
- **Design**
  - **Open-label**, randomized, controlled, parallel group, phase IV non inferiority trial

- **Sample size**
  - Expectations
    - ✓ 85% of participants would achieve the primary outcome
    - ✓ 5% of participants would present secondary exclusion criteria
  - non-inferiority **margin of 12%** and balanced group size
  - **power 80%** and a **one-sided alpha risk of 0.025**

→ 315 patients to be enrolled

Primary objective, efficacy endpoints

Primary objective

- To compare the therapeutic **efficacy** of cefazolin *vs* cloxacillin at **day 90**

Primary endpoint; the therapeutic success

- composite criterion:
  - **Survival at day 90**
  - **Bacteriologic success at day 3 or day 5**
    - ✓ negative set of blood culture
  - **Absence of bacteriological relapse at day 90**
    - ✓ Same *S. aureus* strain than the one isolated at inclusion
  - **Clinical cure at day 90**
    - ✓ Resolution of all symptoms and signs related to the infection

Secondary objectives, safety endpoints

To compare

- The occurrence of any adverse events (AE) and severe adverse events (SAE) at
  - **Day 7**
  - **End of studied antibiotic therapy (EoST)**
  - **End of all antibiotic therapy (EoAT)**
- To compare the rate of **premature discontinuation** of studied antibiotic therapy due to the occurrence of an adverse event
- To compare the occurrence of ***C. difficile* infection**

Adverse events

Classified in grades from mild (Grade 1) to Death (Grade 5) following the CTCAE of the NIH

Severe adverse events

Coded using the MedDRA of the ICH

Acute kidney injury

✓ Increase in serum creatinine by ≥ 26.5 µ mol/L) in 48 h

or

✓ Increase in serum creatinine to ≥1.5 times baseline

or

✓ Urine volume <0.5 mL/kg/h for 6 hours

CTCAE; The Common Terminology Criteria for Adverse Events CTCAE (v4.0) of the National Institutes of Health and National Cancer Institute https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

MedDRA System Organ Classes or Preferred Terms. https://www.meddra.org

Medical Dictionary for Regulatory Activities of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Study population

Inclusion criteria

- Age above 18 years
- Positive blood culture for Gram-positive cocci and a time-to-positivity ≤ 20 h
- At least one set of blood culture positive to MSSA identified by geneXpert PCR

Exclusion criteria

- Antimicrobial therapy active against MSSA in the 72 hours preceding randomisation
- Polymicrobial bacteraemia (excluding contaminants)
- Need for another antibiotic therapy which could not be ceased or substituted by study treatment
- Long-term intravascular devices
- Any material suspected to be infected, or with planned antibiotic treatment exceeding 70 days
- Clinical signs suggestive of a recent stroke, brain abscess, or meningitis
- Stage 4 renal failure (eGFR < 30 mL/min)
- Pre-existing coagulopathy and a prothrombin time <50% not due to anticoagulant treatment
- Previous type 1 or grade 3/4 hypersensitivity reaction to β-lactams
- Limitation of care, or a projected life expectancy lower than 90 days
- Pregnant or breast-feeding women
- Participants under guardianship or trusteeship
- Absence of affiliation to the French Health insurance
- Already participation in another interventional clinical research evaluating a medicinal product

Secondary exclusion criteria

- Meningitis or brain abscess
- Multiple bacterial infection

Bacteriological methods (all strains)

Strains characterized in the French National Reference Centre for *Staphylococci*

- **Whole genome sequencing** (Illumina - 2x 150 bp paired-end reads)

  - **Multilocus sequence typing** (MLST):
    - https://github.com/tseemann/mlst
    - Assignment to clonal complexes

  - ***blaZ* gene determination and characterization**
    - ABRicate (https://github.com/tseemann/abricate) and AMRFinderPlus databases
    - *blaZ* types (A,B,C,D) using PointFinder

Statistical analyses

Primary endpoint (ITT & PP)

- Missing data were imputed using multiple imputation by chain equations method
- Non-inferiority was based on the lower bound of the 95% CI of the difference of proportions of patients with therapeutic success at day 90, after multiple imputation

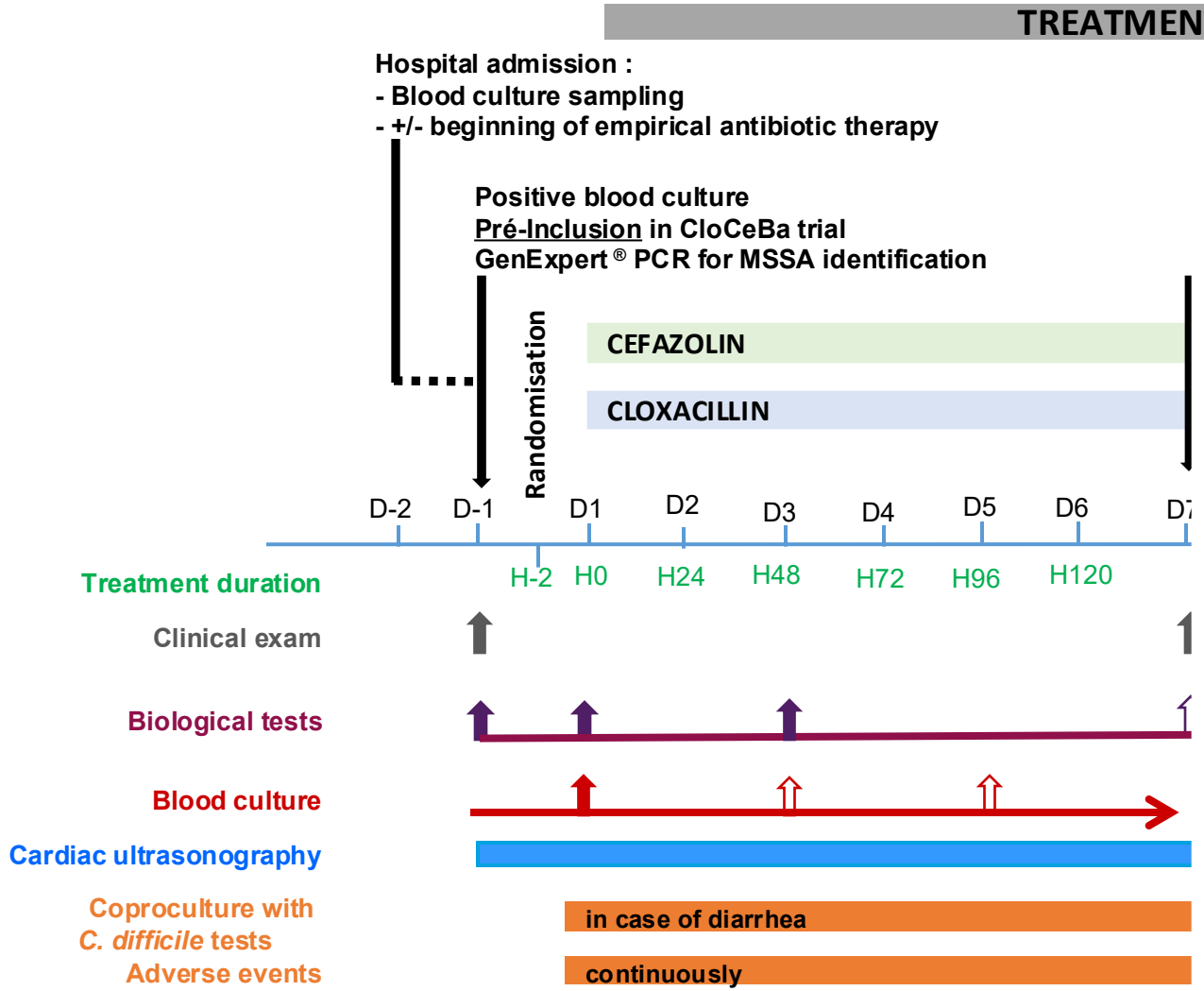
Secondary efficacy (ITT) and safety endpoints (mITT)

- Logistic regression model for categorical variables
- Student's t-test for continuous variables

Definition of populations

- **ITT population**: all randomised participants, maintaining each patient on the group assigned by randomisation whether they received the treatment assigned by randomisation or not.
- **Modified ITT population**: participants from the intention-to-treat population who received at least one dose of the treatment allocated by randomisation
- **PP population**: all participants who received a ≥7-day course of intravenous cefazolin or cloxacillin from inclusion (whatever the treatment assigned by randomisation) and whose total antibiotic treatment lasted at least 14 days

Research schedule and experimental plan



Experimental group

cefazolin *administered by IV route*
25 to 50 mg/kg every ***8 hours, maximum 6 g/day***

Adaptation for GFR between 50-30 mL/min (SPC)
Administered as a 30-minute infusion

VS

Control group

cloxacillin *by IV route*
25 to 50 mg/kg every ***6 hours, maximum 12 g/day***

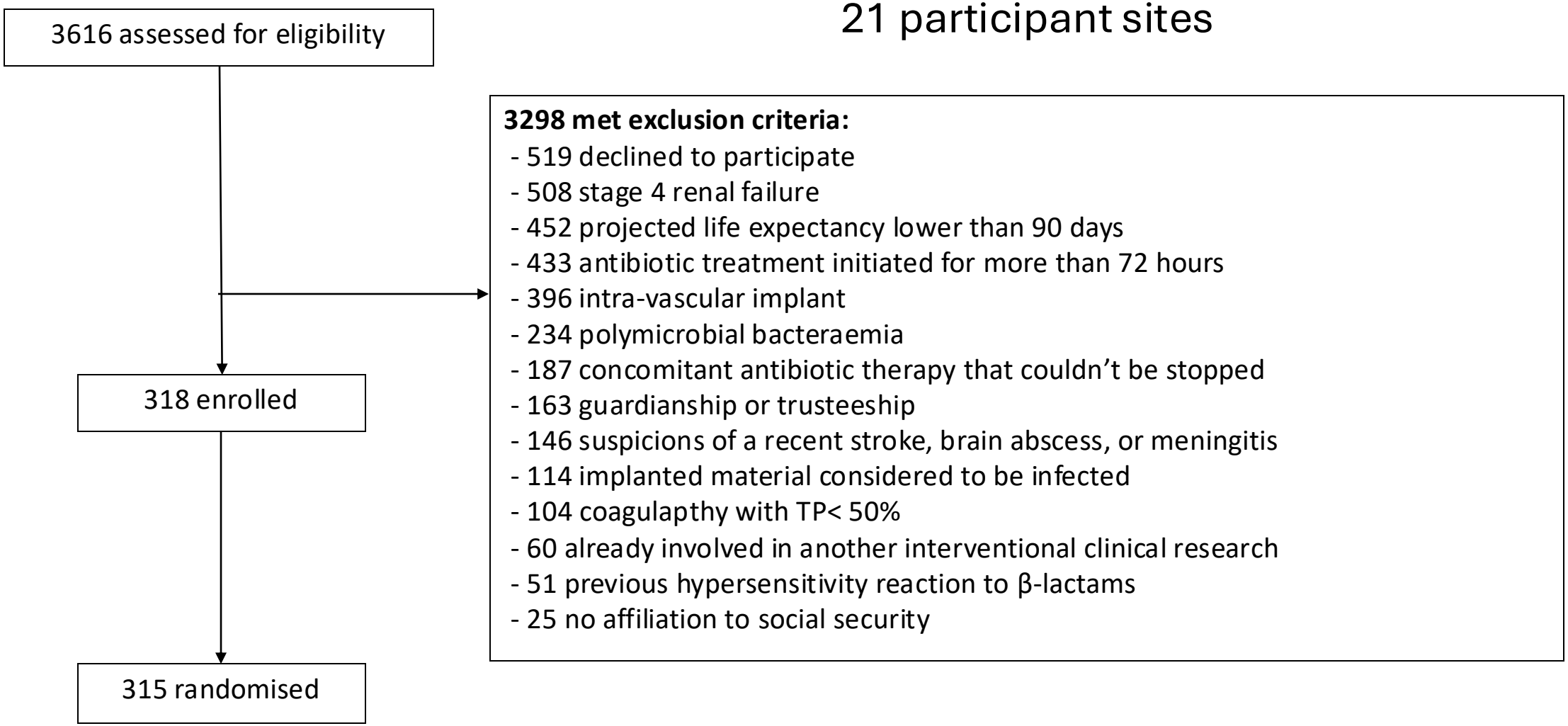
Adaptation for GFR between 60-30 mL/min
AND hepatic dysfunction (SPC)
Administered as a 30-minute infusion

Summary of Product Characteristics

Flow chart

September, 5th 2018 - November, 16th 2023

21 participant sites



Flow chart

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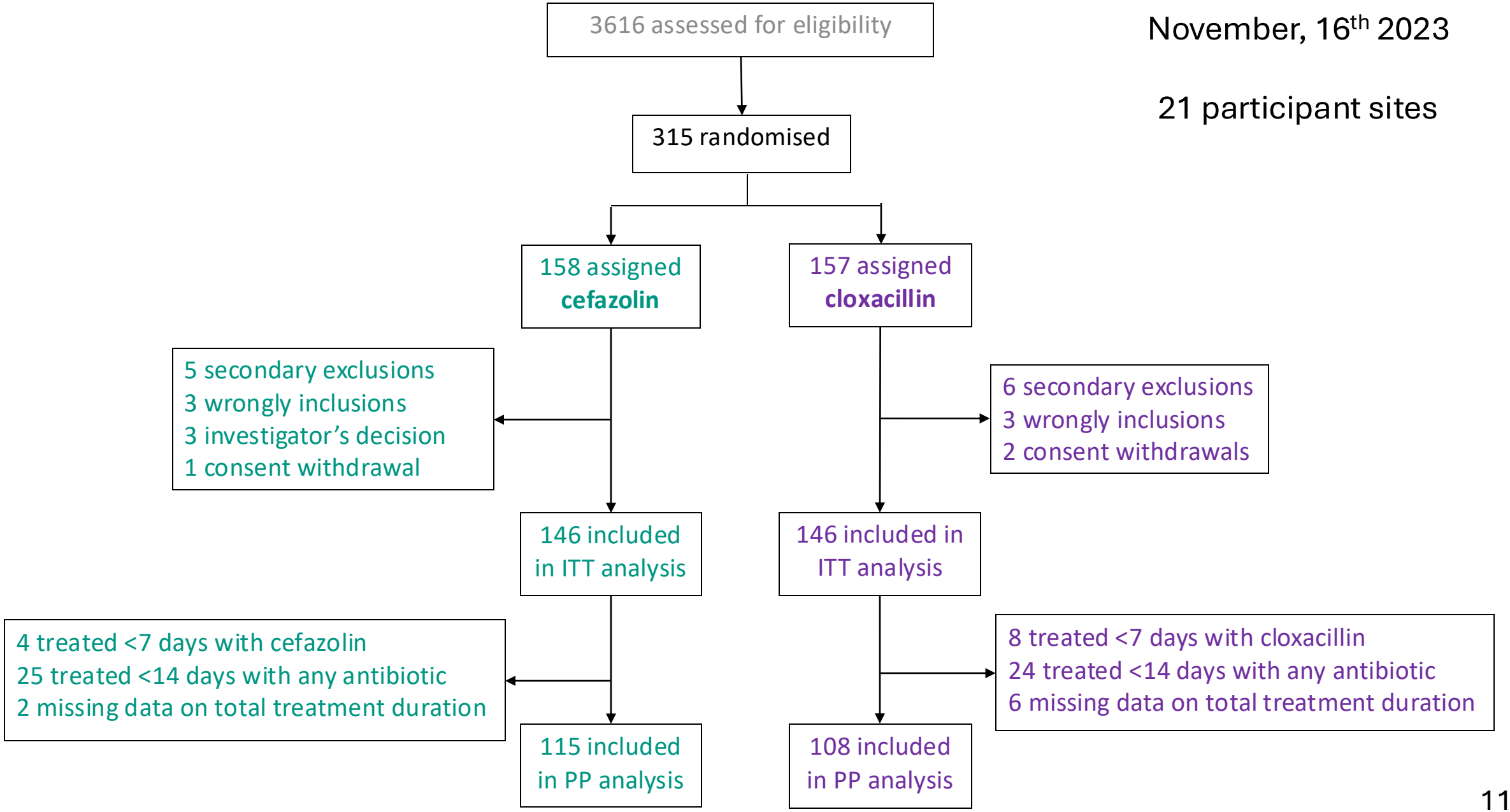


Baseline characteristics of participants, ITT population

	Overall (N=292)	Cefazolin (N=146)	Cloxacillin (N=146)
Age, years (SD)	62.7 (16.4)	62.7 (15.3)	62.8 (17.4)
Male sex (%)	215/292 (73.6)	106/146 (74)	107/146 (73.3)
Charlson comorbidity score (SD)	4.4 (3.1)	4.4 (3.2)	4.3 (3)
At least one comorbid condition (%)	205/291 (70.4)	100/146 (68.5)	105/145 (72.4)
Vascular disease (%)	43/291 (14.8)	24/146 (16.4)	19/145 (13.1)
Chronic pulmonary disease (%)	24/291 (8.2)	12/146 (8.2)	12/145 (8.3)
Moderate or severe liver disease (%)	30/291 (10.3)	17/146 (11.6)	13/145 (9.0)
Diabetes (%)	73/291 (25.1)	42/146 (28.8)	31/145 (21.4)
Moderate or severe renal disease (%)	42/291 (14.4)	21/146 (14.4)	21/145 (14.5)
Solid tumor or leukemia, in past 5 years (%)	75/291 (25.8)	38/146 (26.0)	37/145 (25.5)
AIDS (%)	4/291 (1.4)	2/146 (1.4)	2/145 (1.4)

Baseline characteristics of participants, ITT population

	Overall (N=292)	Cefazolin (N=146)	Cloxacillin (N=146)
History of intravenous drug use (%)	8/292 (2.7)	5/146 (3.4)	3/146 (2.1)
Immunosuppresion (%)	83/292 (28.4)	45/146 (30.8)	38/146 (26)
Treatment with corticosteroids (>5mg/d for > 1W) (%)	20/292 (6.8)	12/146 (8.2)	8/146 (5.5)
Treatment with cancer chemotherapy (%)	49/292 (16.8)	24/146 (16.4)	25/146 (17.1)
Treatment with other immunosuppressive therapy (%)	20/292 (6.8)	12/146 (8.2)	8/146 (5.5)
Solid organ transplantation or HSCT (%)	9/292 (3.1)	7/146 (4.8)	2/146 (1.4)
Prostetic joint (%)	24/292 (8.2)	6/146 (4.1)	18/146 (12.3)
Other medical device (%)	27/292 (9.2)	10/146 (6.8)	17/146 (11.6)
Hospital stay in the year before randomization (%)	154/292 (52.7)	75/146 (51.4)	79/146 (54.1)
Surgery in the year before randomization (%)	74/292 (25.3)	34/146 (23.3)	40/146 (27.4)

Characteristics at base-line of the MSSA bactaeremia ITT population

	Overall (N=292)	Cefazolin (N=146)	Cloxacillin (N=146)
Pitt bacteraemia score (SD)	0.2 (0.6)	0.2 (0.7)	0.2 (0.5)
ICU admission at inclusion	13/223 (5.8)	5/115 (4.3)	8/108 (7.4)
Bacteriological data at inclusion			
Blood culture time-to-positivity, hours	14.4 (5.3)	14.8 (6.1)	14.1 (4.4)
Biological data at inclusion			
Estimated GFR, mL/min	87.9 (27.8)	87.9 (29.2)	87.9 (26.4)
SGOT, UI/L	47.2 (50.6)	45.2 (35.2)	49.3 (63.1)
SGPT, UI/L	47.4 (60.6)	46.2 (53.3)	48.8 (67.7)
Prothrombin Time, % of control	80.1 (17.4)	80.8 (17.1)	79.4 (17.7)
C-reactive protein, mg/L	161.9 (110.2)	163.1 (107.8)	160.7 (113.2)

Characteristics at D7 of the MSSA bactaeremia ITT population

	Overall (N=292)	Cefazolin (N=146)	Cloxacillin (N=146)
Catheter-associated bacteraemia (%)	103/284 (36.3)	52/142 (36.6)	51/142 (35.6)
Bacteraemia of unknown origin (%)	85/284 (29.9)	43/142 (30.3)	42/142 (29.6)
arthritis, osteitis or osteoarthritis (%)	70/284 (24.6)	30/142 (21.1)	40/142 (28.2)
Skin and soft-tissue infection (%)	62/284 (21.8)	26/142 (18.3)	36/142 (25.4)
abscess, deep infection (%)	24/284 (8.5)	9/142 (6.3)	15/142 (10.6)
Urinary infection (%)	17/284 (6)	10/142 (7)	7/142 (4.9)
Infective endocarditis (%)	14/285 (4.9)	8/142 (5.6)	6/143 (4.2)
Respiratory infection (%)	12/284 (4.2)	5/142 (3.5)	7/142 (4.9)

Antibiotic treatments received, ITT population

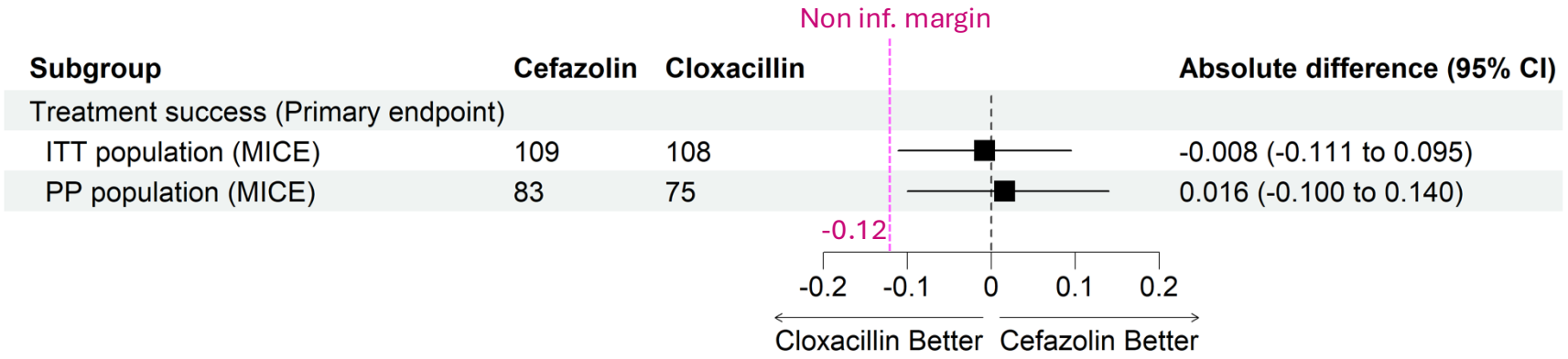
	Overall (N=292)	Cefazolin (N=146)	Cloxacillin (N=146)
Treatments received before randomization			
Antibiotic treatment before randomization (%)	271/292 (92.8)	139/146 (95.2)	132/146 (90.4)
Duration of antibiotic treatment before randomization, days (SD)	1.6 (0.8)	1.6 (0.8)	1.7 (0.8)
Treatments received after randomization			
Duration of the allocated treatment, days (SD)	12.2 (7.4)	12.9 (8.2)	11.6 (6.5)
Total duration of antibiotic treatment, days (SD)	27.2 (19.6)	27.4 (19.6)	27.0 (19.5)

Genetic characteristics of the *Staphylococcus aureus* strains

ITT population

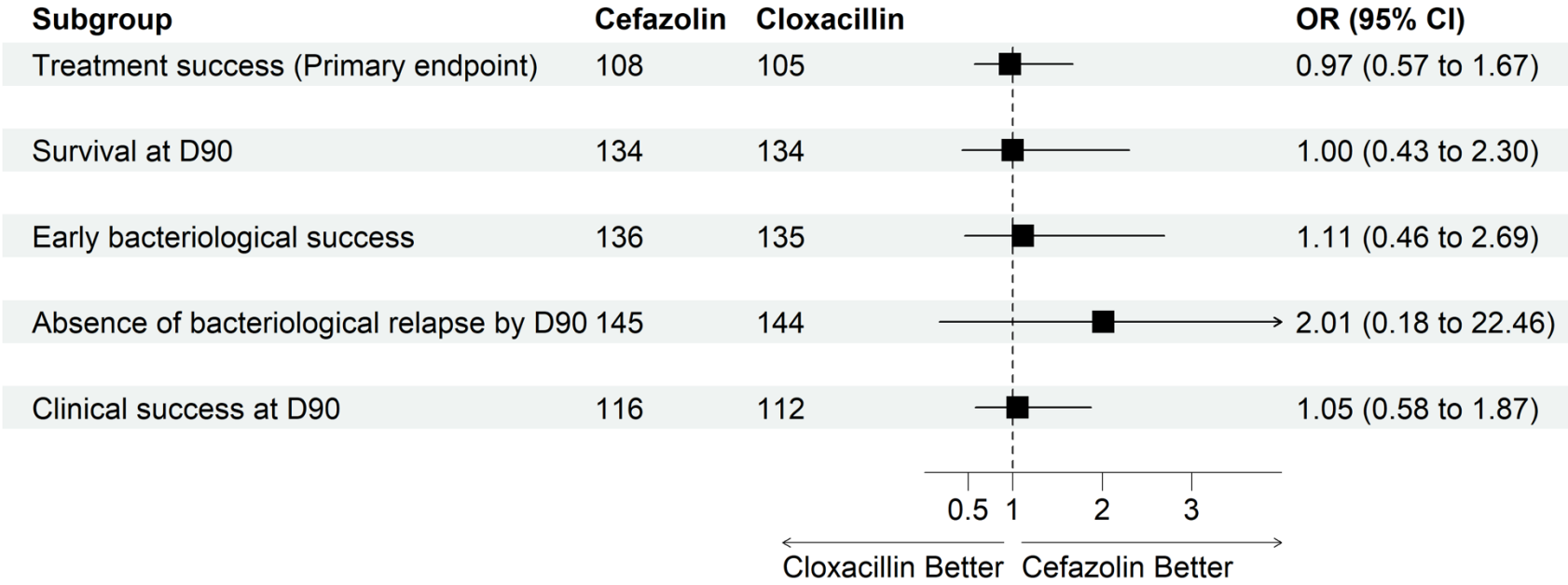
	Overall (N=253)	Cefazolin (N=129)	Cloxacillin (N=124)
blaZ gene			
Absent (%)	75/253 (29.6)	40/129 (31)	35/124 (28.2)
Present (%)	178/253 (70.4)	89/129 (69)	89/124 (71.8)
blaZ allele			
A (%)	58/178 (32.6)	30/89 (33.7)	28/89 (31.5)
B (%)	63/178 (35.4)	40/89 (44.9)	23/89 (25.8)
C (%)	55/178 (30.9)	19/89 (21.3)	36/89 (40.4)
D (%)	2/178 (1.1)	0/89 (0)	2/89 (2.2)

Primary outcome: treatment success



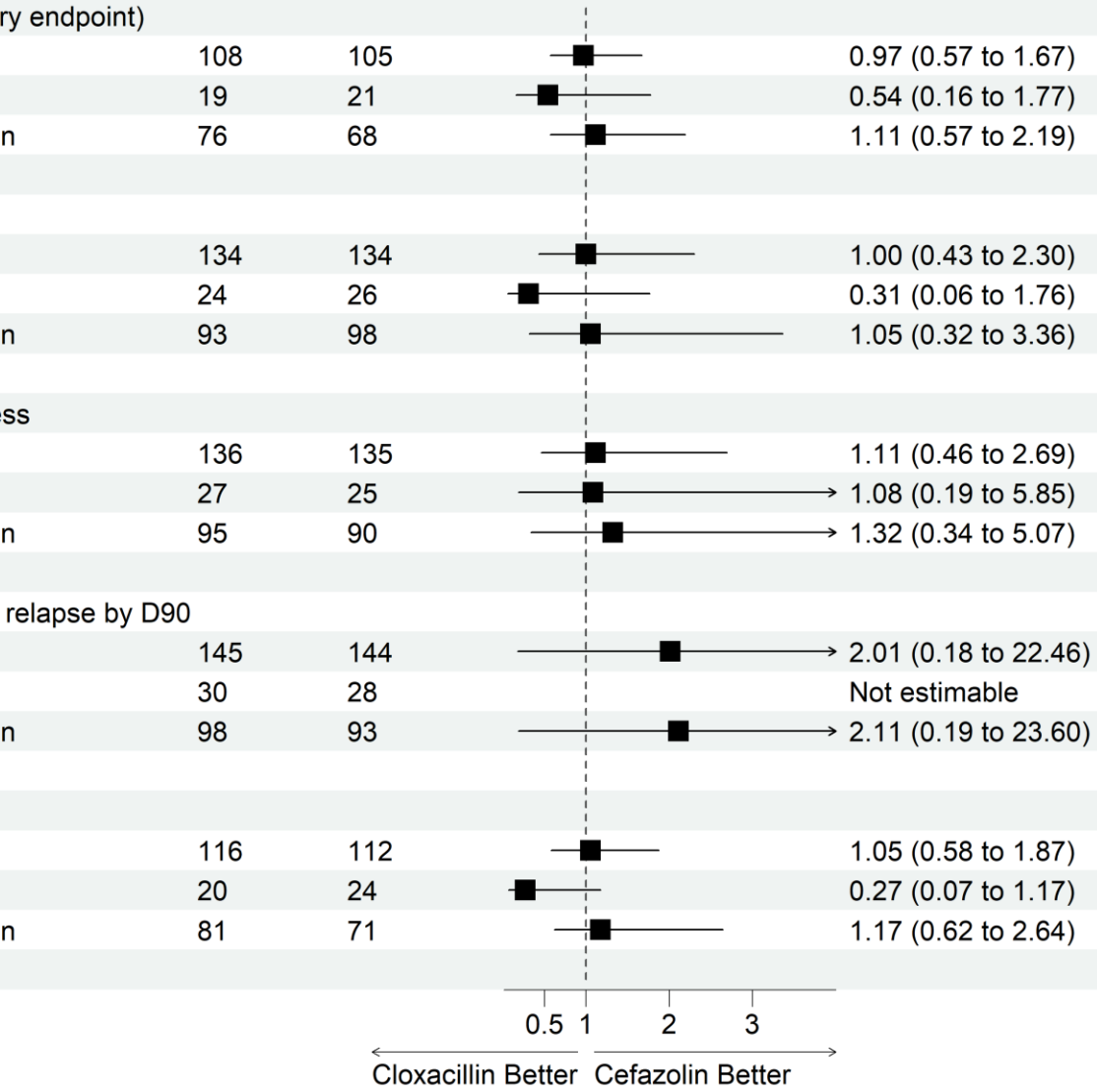
75% cefazolin vs 75.5% cloxacillin

72.2% cefazolin vs 70.1% cloxacillin



Subgroup analyses of the efficacy regarding the BlaZ genes distribution ITT population

Subgroup	Cefazolin	Cloxacillin	OR (95% CI)
Treatment success (Primary endpoint)			
All Participants	108	105	0.97 (0.57 to 1.67)
Subgroup: blaz A strain	19	21	0.54 (0.16 to 1.77)
Subgroup: no blaz A strain	76	68	1.11 (0.57 to 2.19)
Survival at D90			
All Participants	134	134	1.00 (0.43 to 2.30)
Subgroup: blaz A strain	24	26	0.31 (0.06 to 1.76)
Subgroup: no blaz A strain	93	98	1.05 (0.32 to 3.36)
Early bacteriological success			
All Participants	136	135	1.11 (0.46 to 2.69)
Subgroup: blaz A strain	27	25	1.08 (0.19 to 5.85)
Subgroup: no blaz A strain	95	90	1.32 (0.34 to 5.07)
Absence of bacteriological relapse by D90			
All Participants	145	144	2.01 (0.18 to 22.46)
Subgroup: blaz A strain	30	28	Not estimable
Subgroup: no blaz A strain	98	93	2.11 (0.19 to 23.60)
Clinical success at D90			
All Participants	116	112	1.05 (0.58 to 1.87)
Subgroup: blaz A strain	20	24	0.27 (0.07 to 1.17)
Subgroup: no blaz A strain	81	71	1.17 (0.62 to 2.64)



Severe adverse events and safety outcomes mITT population

	Overall	Cefazolin (N=146)	Cloxacillin (N = 146)	OR [95%CI]	P-value
Any SAE over the study course	114/292 (39%)	50/146 (34.2%)	64/146 (43.8%)	0.67 [0.42; 1.08]	0.093
Any SAE by day 7	44/292 (15.1%)	14/146 (9.6%)	30/146 (20.5%)	0.41 [0.21; 0.81]	0.0089
Any SAE by end of study treatment	60/292 (20.5%)	21/146 (14.4%)	39/146 (26.7%)	0.46 [0.25; 0.83]	0.0091
Any SAE by end of antimicrobial therapy	78/292 (26.7%)	31/146 (21.2%)	47/146 (32.2%)	0.57 [0.34; 0.97]	0.034

Severe adverse events and safety outcomes mITT population

	Overall	Cefazolin (N=146)	Cloxacillin (N = 146)	OR [95%CI]	P-value
Any SAE over the study course	114/292 (39%)	50/146 (34.2%)	64/146 (43.8%)	0.67 [0.42; 1.08]	0.093
Any SAE by day 7	44/292 (15.1%)	14/146 (9.6%)	30/146 (20.5%)	0.41 [0.21; 0.81]	0.0089
Any SAE by end of study treatment	60/292 (20.5%)	21/146 (14.4%)	39/146 (26.7%)	0.46 [0.25; 0.83]	0.0091
Any SAE by end of antimicrobial therapy	78/292 (26.7%)	31/146 (21.2%)	47/146 (32.2%)	0.57 [0.34; 0.97]	0.034
By end of study treatment					
Renal and urinary disorders	9/292 (3.1%)	0/146 (0.0%)	9/146 (6.2%)	NE	0.003
Acute kidney injury	9/292 (3.1%)	0/146 (0.0%)	9/146 (6.2%)	NE	0.003
Nervous system disorders	4/292 (1.4%)	1/146 (0.7%)	3/146 (2.1%)	0.33 [0.03; 3.2]	0.622
Hepatobiliary disorders	4/292 (1.4%)	2/146 (1.4%)	2/146 (1.4%)	1.0 [0.14; 7.2]	1
Hepatic cytolysis	3/292 (1.0%)	1/146 (0.7%)	2/146 (1.4%)	0.5 [0.04; 5.54]	1
Blood and lymphatic system disorders	2/292 (0.7%)	1/146 (0.7%)	1/146 (0.7%)	1.0 [0.06; 16.14]	1
Haemophilia	0/292 (0.0%)	0/146 (0.0%)	0/146 (0.0%)	NE	NA
Skin and subcutaneous tissue disorders	3/292 (1.0%)	0/146 (0.0%)	3/146 (2.1%)	NE	0.25
Cutaneous allergy	2/292 (0.7%)	0/146 (0.0%)	2/146 (1.4%)	NE	0.5

Severe adverse events and safety outcomes mITT population

	Overall	Cefazolin (N=146)	Cloxacillin (N = 146)	OR [95%CI]	P-value
Any SAE over the study course	114/292 (39%)	50/146 (34.2%)	64/146 (43.8%)	0.67 [0.42; 1.08]	0.093
Any SAE by day 7	44/292 (15.1%)	14/146 (9.6%)	30/146 (20.5%)	0.41 [0.21; 0.81]	0.0089
Any SAE by end of study treatment	60/292 (20.5%)	21/146 (14.4%)	39/146 (26.7%)	0.46 [0.25; 0.83]	0.0091
Any SAE by end of antimicrobial therapy	78/292 (26.7%)	31/146 (21.2%)	47/146 (32.2%)	0.57 [0.34; 0.97]	0.034
By end of study treatment					
Renal and urinary disorders	9/292 (3.1%)	0/146 (0.0%)	9/146 (6.2%)	NE	0.003
Acute kidney injury	9/292 (3.1%)	0/146 (0.0%)	9/146 (6.2%)	NE	0.003
Nervous system disorders	4/292 (1.4%)	1/146 (0.7%)	3/146 (2.1%)	0.33 [0.03; 3.2]	0.622
Hepatobiliary disorders	4/292 (1.4%)	2/146 (1.4%)	2/146 (1.4%)	1.0 [0.14; 7.2]	1
Hepatic cytolysis	3/292 (1.0%)	1/146 (0.7%)	2/146 (1.4%)	0.5 [0.04; 5.54]	1
Blood and lymphatic system disorders	2/292 (0.7%)	1/146 (0.7%)	1/146 (0.7%)	1.0 [0.06; 16.14]	1
Haemophilia	0/292 (0.0%)	0/146 (0.0%)	0/146 (0.0%)	NE	NA
Skin and subcutaneous tissue disorders	3/292 (1.0%)	0/146 (0.0%)	3/146 (2.1%)	NE	0.25
Cutaneous allergy	2/292 (0.7%)	0/146 (0.0%)	2/146 (1.4%)	NE	0.5
Premature discontinuation of study ttt due to an AE	18/292 (6.2%)	5/146 (3.4%)	13/146 (8.9%)	0.36 [0.12; 1.04]	0.15
Clostridioides difficile infection	6/292 (2.1%)	3/146 (2.1%)	3/146 (2.1%)	1.00 [0.20; 5.04]	>0.99

Classification of renal serious adverse events mITT population

	Overall (N = 292)	Cefazolin (N = 146)	Cloxacillin (N = 146)	OR [95%CI]	P-value
By day 7					
Renal and urinary disorders	7/292 (2.4)	0/146 (0)	7/146 (4.8)	NE	0.015
Acute kidney injury	7/292 (2.4)	0/146 (0)	7/146 (4.8)	NE	0.015
By EoST					
Renal and urinary disorders	9/292 (3.1)	0/146 (0)	9/146 (6.2)	NE	0.003
Acute kidney injury	9/292 (3.1)	0/146 (0)	9/146 (6.2)	NE	0.003
By EoAT					
Renal and urinary disorders	12/292 (4.1)	2/146 (1.4)	10/146 (6.8)	0.19 [0.04; 0.88]	0.035
Acute kidney injury	12/292 (4.1)	2/146 (1.4)	10/146 (6.8)	0.19 [0.04; 0.88]	0.035
Creatinine change over time					
Creatinine change at day 7, µmol/L	-2.3 (38)	-13 (19.6)	8.9 (48.2)	-	<0.0001
Creatinine change at end of study treatment, µmol/L	6.3 (68.8)	-4.7 (62.7)	18.8 (73.5)	-	<0.0001

Discussion and conclusion

- Cefazolin has a **non-inferior efficacy** than cloxacillin for the treatment of MSSA bacteriemia with a **better safety profile**
- Margin of error of 12% as a limitation
- Representativeness of the study population
- Traditional RCT *vs* adaptive platform (SNAP)
- Next steps : deep analysis of BLAZ possible impact in high bacterial inoculum infections

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