Infect Dis Ther (2025) 14:643–655
https://doi.org/10.1007/s40121-025-01110-9

STUDY PROTOCOL

Oral vs. Outpatient Parenteral Antimicrobial Treatment for Infective Endocarditis: Study Protocol for the Spanish OraPAT-IE GAMES Trial

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Received: October 30, 2024 / Accepted: January 23, 2025 / Published online: March 1, 2025

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Prior Presentation: The OraPAT-IE GAMES trial opened its first site of recruitment in April 2022. The first patient was enrolled in August 2022. Preliminary data on patient recruitment for this study were presented in poster format at the 17th International Society of Infectious Cardiovascular Diseases (ISCVID) Symposium held in June 16–18, 2024, in Malmö, Sweden; and as an oral presentation at the 13th Congress of the Sociedad Española de Infecciones Cardiovasculares (SEICAV) held in November 22–23, 2024 in Bilbao, Spain. The abstract presented at both conferences (with updated preliminary recruitment data) can be seen as Appendix C of the supplementary material. The recruitment period has been extended until the end of 2026.

OraPAT-IE GAMES Investigators are listed in acknowledgements section.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-025-01110-9.

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ABSTRACT

Introduction: The POET trial demonstrated that moving from intravenous to oral antibiotics in stable patients with left-sided infective endocarditis (IE) was noninferior to fully parenteral treatment. However, it did not compare outpatient strategies.

Methods: The OraPAT-IE GAMES trial is a non-inferiority, multicenter, randomized, open-label study aimed to compare partial oral versus outpatient parenteral antibiotic therapy (OPAT) for consolidation of antibiotic treatment in left-sided IE. A total of 342 stable patients with IE caused by selected micro-organisms will eventually be included. After a minimum of 10 days of parenteral treatment, stable patients

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are randomized to oral therapy or OPAT. The primary end-point is a composite of all-cause mortality, unplanned cardiac surgery, relapse of positive blood cultures and/or unplanned hospital admission. Patients are followed-up for 6 months after completing antibiotic therapy.
Planned Outcome: This trial seeks to demonstrate the equivalent efficacy of the two outpatient strategies currently available for stable patients with IE in the consolidation phase of antibiotic treatment.
Conclusion: In a global context of limited healthcare resources and a sustained increase in elderly and frail patients, it is of great importance to demonstrate the effectiveness and safety of outpatient management strategies that could reduce the duration of conventional hospitalizations with their potential complications and inherent costs.
Trial Registration: EudraCT: 2020-001024-34. ClinicalTrials.gov identifier: NCT05398679.

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Keywords: Randomized controlled trial; Infective endocarditis; Mortality; Oral antibiotic therapy; Oral step-down antibiotic treatment; Partial oral treatment; OPAT; Outpatient parenteral antibiotic treatment; Reinfections; Relapses

Key Summary Points

The OraPAT-IE GAMES is the first randomized clinical trial to compare the two outpatient strategies available for patients with stable infective endocarditis in the consolidation phase of antibiotic treatment.

Although the planned sample size is large (n = 342), it will be carried out in 20 hospitals within the multicenter and multidisciplinary GAMES study group, so it is considered feasible.

This study will presumably share the inherent limitations of its open label design. Furthermore, the trial will evaluate oral versus parenteral antibiotic therapy strategies but will not be powered to demonstrate differences between various subgroups of IE (e.g., native valve IE, prosthetic valve IE, specific micro-organisms, etc.).

Beyond the aforementioned limitations, this study could have a relevant impact on clinical practice, improving the quality of life of patients and allowing the shortening of conventional hospitalizations with their inherent complications and costs.

INTRODUCTION

Although infective endocarditis (IE) is a rare infectious disease, with crude annual incidence rates ranging between 1.5 and 9.0 cases per 100,000 people, mortality has remained relatively stable at around 20% during hospitalization, and more than 30% per year [1]. In Spain, the crude annual incidence is estimated at around 3 cases per 100,000 people, showing a slight but constant increase [2]. This incidence represents approximately 1600 new cases of IE per year in our country.

Some classic recommendations for the treatment of IE have remained stable and valid for decades. These include: (1) the need for prolonged antimicrobial therapy (4–6 weeks); (2)

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parenteral administration; (3) with bactericidal antimicrobials; and (4) in hospitalized patients, given the high complexity of its management. In fact, all these recommendations are still valid in the most recent American and European guidelines [3, 4]. However, the need for a prolonged hospital stay predisposes patients to nosocomial complications, such as colonization with resistant microbiological flora and nosocomial infections, and, furthermore, its association with a marked deterioration in functional status has been observed in geriatric patients [5]. Additionally, this increases costs and limits the availability of beds for patients in tertiary centers. Outpatient parenteral antibiotic therapy (OPAT) has been shown to be effective and safe for the treatment of infective endocarditis (IE) in selected cases [6–11]. However, until recently, most infectious disease guidelines had restrictive criteria for OPAT for this disease. In a work published by the GAMES group (Grupo de Apoyo al Manejo de la Endocarditis en España), it was concluded that these recommendations could be greatly expanded [12].

On the other hand, a parenteral route can be a source of serious complications (e.g., thrombosis or bacteremia). Additionally, intravenous antibiotics are generally expensive. Oral antibiotic therapy could reduce these complications and be an appropriate alternative, but experience with left-sided endocarditis was limited to small series and cohort studies [13]. The large POET randomized clinical trial published in 2019 demonstrated that a significant proportion of patients with left-sided IE could benefit from oral antibiotic therapy, with efficacy and safety comparable to parenteral treatment [14]. In this trial, however, all patients in the parenteral arm and most of those included in the oral arm, completed their treatment regimens in conventional hospitalization. To date, no trial has compared the efficacy and safety of OPAT versus outpatient oral therapy for this group of well-selected patients.

The OraPAT-IE GAMES trial (ClinicalTrials.gov ID: NCT05398679), currently recruiting, may provide the necessary evidence to choose one modality over another and to identify specific groups that may benefit more from one of these strategies. We aimed to demonstrate the non-inferiority of oral outpatient antibiotic therapy in comparison with OPAT. As secondary objectives, we will compare the quality of life of patients included in both arms, the costs of interventions through a pharmaco-economic sub-study, and the complications related to parenteral and oral administration of antibiotics (such as antibiotics or catheter-related adverse events and superinfections, e.g., *Clostridioides difficile* diarrhea).

METHODS

Study Design

The OraPAT-IE GAMES study is a nationwide, noninferiority, multicenter, prospective, randomized, controlled, open, non-inferiority (delta 10%) clinical trial. Randomization will be done 1:1 and will be performed online through a centralized computer system.

Eligible Patients

Patients included in the study must meet all the following inclusion criteria: (1) left-sided native or prosthetic definite infective endocarditis based on the modified Duke criteria infected with one of the following non-resistant microorganisms: non-resistant streptococci and other Gram positive cocci, e.g., *Granulicatella* and *Abiotrophia*, *Enterococcus faecalis, Staphylococcus aureus*, coagulase-negative staphylococci, and HACEK group (*Haemophilus* spp., *Aggregatibacte*r spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp); (2) ≥ 18 years old; (3) ≥ 10 days of appropriate parenteral antibiotic treatment overall and at least 1 week of appropriate parenteral treatment after valve surgery (a positive valve culture change the overall duration of treatment, but not affecting the patient's eligibility); (4) T < 38.0 °C for more than 2 days; (5) C-reactive protein that dropped below 25% of the peak value or below an absolute value of 20 mg/L, and the white blood cell count dropped to less than 15×10^9/L during antibiotic treatment; (6) no sign of abscess formation revealed by echocardiography; and (7)

transthoracic (TTE) and/or transoesophageal echocardiography (TEE) performed preferably within 48 h of randomization (TEE is not mandatory if TTE is of good and reassuring quality). Echoscopy (portable echocardiograms) are also admitted, as long as they are registered on the clinical history.

Exclusion Criteria

(1) Body mass index > 40; (2) concomitant infection requiring intravenous antibiotic therapy; (3) inability to give informed consent to participation; (4) suspicion of reduced absorption of oral treatment due to abdominal disorder; (5) micro-organisms other than those defined in inclusion criteria; (6) any immunosuppressive disease or any medical condition at the discretion of the investigator that may preclude oral or OPAT therapy; (7) no family or appropriate home support; (8) reduced compliance; (9) women of childbearing potential with a positive pregnancy test, or participants (male or female) who wish to plan a pregnancy during the trial period; and (10) women in lactancy period.

Setting

The study is being carried out in 20 Spanish university hospitals, coordinated by the Hospital Clinic de Barcelona: Hospital de Sant Pau I la Santa Creu, Barcelona; Hospital Universitario de Bellvitge, Barcelona; Hospital Virgen del Rocío, Sevilla; Hospital Virgen Macarena, Sevilla; Hospital Gregorio Marañón, Madrid; Hospital de Cruces, Bilbao; Hospital de Donostia, Guipuzkoa; Hospital San Pedro, Logroño; Hospital Marqués de Valdecilla, Santander; Hospital Universitario de Canarias, Tenerife; Hospital Son Espases, Palma Mallorca; Consorci Sanitari Parc Taulí de Sabadell, Barcelona; Hospital General Universitario de Alicante, Alicante; Hospital Universitario La Paz, Madrid; Hospital Clínico Universitario Virgen de la Arrixaca, Murcia; Hospital Universitario y Politécnico La Fe, Valencia; Hospital Universitari Mútua Terrassa, Terrassa, Barcelona; Hospital Universitario Ramón y Cajal, Madrid; and Hospital del Mar, Barcelona.

Intervention

The initial parental IE treatment will be in accordance with the European guidelines [8]. Selected patients (n = 342) with left-side IE and specific microorganisms (*Staphylococcus aureus*, coagulase negative staphylococci, *Streptococcus* spp., *Enterococcus* spp., and other selected microorganisms), and available oral options will be randomized 1:1 to finish antibiotic therapy on either outpatient parenteral or oral regimens (with two active oral drugs; see Appendix A in the supplementary material). Before randomization, patients will have completed at least 10 days of intravenous therapy, and/or after 7 days in the case of cardiac valvular surgery for IE, and have shown good clinical evolution and no clinical or echocardiographic signs of potential bad prognosis. After randomization, the patient must follow the assigned treatment (oral vs. OPAT) for at least 25% of the total duration of treatment for their endocarditis. Parenteral consolidation treatment in the OPAT regimen arm will be selected at the discretion of the treating physician and following the recommendations of current clinical guidelines. It may consist of conventional antibiotics for daily administration as well as "long-acting" options [4].

Primary Endpoint

The composite endpoint (whatever happen first) consists of unplanned hospitalization due to any reason, all-cause mortality, unplanned cardiac surgery and IE relapse of positive blood cultures with the primary pathogen within 6 months from diagnosis. Unplanned cardiac surgery is defined as surgery of the heart not planned before randomization. Surgery due to sterile pericardial effusion or hemorrhage is, however, not included in this endpoint. Secondary endpoints are patient satisfaction (standardized questionnaires), complications related to parenteral administration and oral administration of antibiotics,e.g., antibiotic adverse reactions,

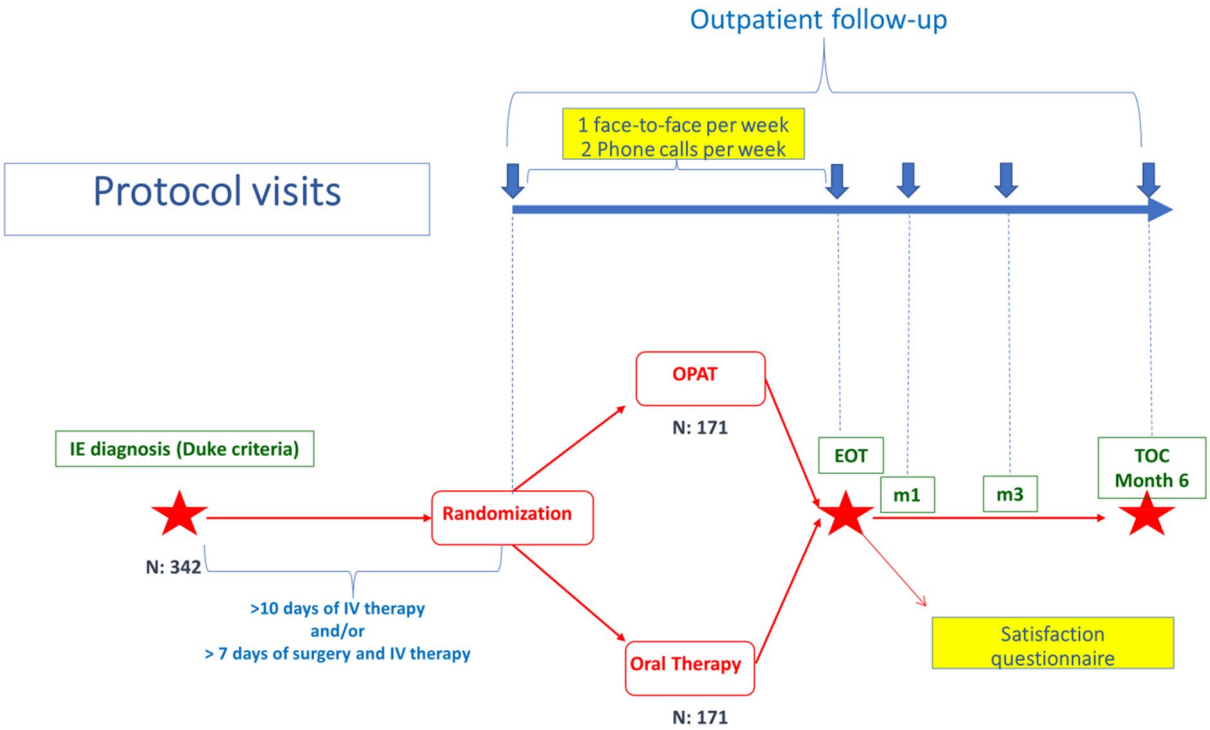

Fig. 1 Study design. *EOT* end of treatment, *IE* infective endocarditis, *IV* intravenous, *m1* first month of follow-up, *m3* third month of follow-up, *OPAT* outpatient parenteral antibiotic treatment, *TOC* test of cure

catheter-related adverse events, e.g., phlebitis and line-related bloodstream infections, and superinfections, e.g., *Clostridioides difficile* diarrhea. Finally, also as a secondary objective of this trial, a cost–efficacy analysis will be conducted to compare healthcare costs in both study arms. Only direct costs will be included and the costs will be estimated from the National health System perspective. The costs that we will include are: staff, pharmacy (drugs and consumables), transportation of staff to patients' homes, diagnostic tests, structural costs, cost of adverse events and catheter complications, emergency room visits, and hospital readmissions [15].

Follow-Up

Patients will be followed up for 6 months after the cessation of antibiotic treatment. Follow-up examinations at 1 and 6 months will include clinical examinations and measurement of white blood cell count, C-reactive protein, and blood cultures (Fig. 1; and trial schedule in Table 1). The follow-up design is aimed to be as similar as possible to normal clinical practice, requesting essential examinations and leaving it up to the treating physicians to request additional studies according to each specific case. Follow-up TTE will also be requested according to the criteria of the treating physicians.

Statistical Analysis Plan

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96). A detailed Statistical Analysis Plan (SAP) agreed upon by the Sponsor and the Project Statistician will be available before the database closure. This SAP will follow the general regulatory recommendations given in the ICHE9 guidance, as well as other specific guidance on methodological and statistical issues. Also, it will stick to

Table 1 The OraPAT-IE GAMES visit schedule and study procedures

	Screen period	Baseline	Nurse regular visits[b]	EOT	Month 1	Month 3	Month 6	Early termination
Eligibility, consent signature	Parenteral antimicrobials according to inclusion criteria	x						
Randomization		x						
Full exam		x						
History, exam and safety evaluation		x	x	x	x	x	x	x
Demographic data		x						
Blood cultures[a]		x		x		x	x	x
Hematology		x	x[c]	x	x	x	x	x
Biochemistry		x	x[c]	x	x	x	x	x
Pregnancy test		x					x	x
Volume of blood (mL)		20 mL	Up to 20 mL	Up to 20 mL	Up to 20 mL	Up to 20 mL	Up to 20 mL	Up to 20 mL
Total volume of blood (mL)								

Biochemistry will include at least glycemia, ionogram, CRP, and creatinine, and all other determinations at the discretion of the investigator. Hematology will include hematocrit, WBC count with differential count and platelets, and all other determinations at the discretion of the investigator

[a]Will be taken at baseline and repeated when clinically indicated until end of treatment (EOT). Other cultures (urine, sputum, etc.) may be considered at the discretion of the investigator

[b]Regular visits are periodical visits, the visit periodicity being defined as for patients with parenteral treatment, as daily visits or every 48 h, with one entry per week recorded in the eCRD. Each center can organize visits according to its usual practice, but at least one telephone control and one weekly face-to-face visit is suggested (the latter must be registered in the eCRD), until the end of the study treatment

[c]When clinically indicated by the investigator team, at least once weekly

the recommendations given by the consensus documents of the scientific journals to improve the reliability and value of medical research literature by promoting transparent and accurate reporting of clinical research studies.

The SAS System (Release 9.4, or an upgraded version), or equivalent validated statistical software, will be the statistical software used to analyze the datasets. A summary of the overall approach to statistical analysis is presented hereafter. The trial is designed as a non-inferiority trial, and hence to determine whether partial oral treatment is non-inferior to OPAT. According to our own rates for the primary endpoint, unplanned hospitalization due to any reason is 12%, including mortality (4.2%), unplanned surgery (5.6%), and relapse of bacteremia (1.4%). A risk difference (i.e., a non-inferiority margin) of 10 percentage points has been chosen. Under the assumption of a 3% loss to follow-up, we determined that inclusion of 342 patients would be required to provide a power of 80% and a level of signification of 0.05 to confirm non-inferiority.

There will be the following analysis populations for this study. *Modified Full Analysis Set (mFAS)*: all patients who are randomized into the study and who have received the investigational medicinal product will be included in the mFAS population. *The Safety population*: the safety population will have the same definition as the mFAS subset and, thus, all safety analysis will be conducted on the mFAS population. *Per Protocol Population*: per protocol patient sets will be defined as those patients included in the mFAS set without major protocol deviations that might impact the study's main assessments. These deviations will be assessed during the data review prior to database lock. An interim analysis is planned to be carried out by an independent DSMB (Data Safety Monitoring Board) upon completion of 25% of the estimated sample size (85 patients).

Monitoring

Adverse event (AE): an AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. The definitions of serious adverse event (SAE) and adverse reaction (AR), and the assessment of its intensity grade as well as the assessment of causality will be defined, registered, documented, and reported according to usual Good Clinical Practice (GCP) procedures. Pharmacovigilance activities will be delegated by the sponsor to a pharmacovigilance center.

Ethics

The trial will be conducted according to the principles of the last Declaration of Helsinki (accorded by the 64th World Medical Association General Assembly in 2013), the GCP, and current legislation. The investigator is responsible for guaranteeing that the clinical trial is realized following the directives established by the International Conference on Harmonization about GCP and local legislation.

The study was authorized by the Spanish Medicines and Healthcare Products Regulatory Agency (Agencia Española de Medicamentos y Productos Sanitarios; AEMPS) and the Clinical Research Ethics Committee. The trial protocol received AEMPS approval on December 15 2021 and the research ethics committee approval on March 8 2022. A substantial amendment received AEMPS approval and Clinical Research Ethics Committee approval on January 25 and February 14 2023, respectively.

The principal investigator or collaborator at each site will provide the information sheets to the patients, and will explain the study and objectives and clarify any doubts. They will obtain written informed consent from all patients, or their legal representatives (LRs) if they lack capacity, before enrolment. Patients (or their LRs) are free to withdraw from the trial

at any time and this will be explicitly stated on the patient's information sheets.

Patient personal and clinical information will be managed according to European Regulation 2016/679 and Spanish legislation. Patient data will be anonymized, identifying every patient by a code. Only the study doctor and collaborators have access to clinical history. Consequently, the patient's identity will not be revealed to any other person, except in cases of medical emergency or if required to do so by law. Access to patient information will be restricted to the study doctor and collaborators, the health authorities (AEMPS), the Clinical Research Ethics Committee, and personnel authorized by the sponsor when they need to check the data and procedures used in the study, but always maintaining the confidentiality of the said information in accordance with current legislation.

DISCUSSION

According to classic recommendations for the treatment of IE, prolonged parenteral antimicrobial therapy is still valid for most patients [3, 4]. However, prolonged hospital stay predisposes patients to nosocomial complications, is associated with a deleterious functional impact in the geriatric population, and, finally, it increases costs and limits the availability of beds in tertiary centers.

Outpatient parenteral antibiotic therapy has never been tested in the setting of a randomized clinical trial. While, intuitively, the efficacy should be equal for OPAT compared to parenteral therapy in an inpatient setting, patients following OPAT therapy may be controlled less frequently that those hospitalized. Our aim is to demonstrate the non-inferiority of outpatient oral antibiotic therapy in comparison with outpatient parenteral antibiotic treatment. As secondary objectives, we will compare the quality of life of patients included in both arms, the costs of interventions through a pharmaco-economic sub-study, and the complications related to parenteral and oral administration of antibiotics (such as catheter-related events or superinfections, e.g., *Clostridioides difficile* diarrhea). Our study therefore starts from a plausible hypothesis and will follow a rigorous methodology that includes the realization of a multicenter randomized clinical trial, with the participation of several university hospitals distributed throughout the country. On the basis outlined above, we consider the OraPAT-IE GAMES study to be feasible, safe, and with potentially relevant implications for clinical practice in the therapeutic approach to infective endocarditis. Many physicians and patients continue to feel more comfortable ending antibiotic treatment for IE by an intravenous route at home [16], but the OPAT option unfortunately still has weaker evidence than the oral one. The OraPAT-IE GAMES trial will provide solid evidence to position this strategy as equivalent.

However, our study has several limitations that must be acknowledged. Firstly, the trial will evaluate the strategies of oral and parenteral antibiotic therapy, but fail to have enough power to demonstrate differences per subgroups (e.g., native valve-IE, prosthetic valve-IE, specific microorganisms) due to the presumed low number for these sub-groups. Unfortunately, the sample sizes required for a specific study for each specific microorganism or indication would make the trial completely unfeasible. Our study, however, aims to compare treatment strategies rather than the treatment approach for specific groups or specific antibiotic combinations. Secondly, it is certainly impossible for patients who complete oral treatment at home to be followed up as closely as patients who complete OPAT treatment (with daily nursing visits), and much less closely as patients who are hospitalized. This limitation is, however, common in other clinical trials comparing oral versus parenteral strategies. It is worth clarifying, however, that the suggested telephone contact is appropriately close to ensure patient safety, and face-to-face visits will be added whenever necessary. Thirdly, although the sample size is large (n = 342), the 20 participating centers have a high volume of endocarditis per year, and we estimate they will be able to include enough patients in this trial. Moreover, centers without OPAT programs are not included in this

trial. Although this could be a limitation due to the lack of generalization of this approach, we think that, if the results show the non-inferiority of the oral antibiotic therapy at home, this could be expanded immediately to all Spanish medical centers. Finally, our study will presumably share the inherent limitations of its open label design.

CONCLUSIONS

In a global context of limited healthcare resources and a sustained increase in elderly and frail patients, it is of great importance to demonstrate the effectiveness and safety of outpatient management strategies that could reduce the duration of conventional hospitalizations with their potential complications and inherent costs. The OraPAT-IE GAMES clinical trial seeks to demonstrate the equivalent efficacy of the two outpatient strategies currently available for stable patients with infective endocarditis.

ACKNOWLEDGEMENTS

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Author Contributions. Juan Ambrosioni, Guillermo Cuervo and José M. Miró conceived and designed the study. Guillermo Cuervo and José M. Miró wrote and revised the manuscript. All authors have read and approved the final manuscript.

Funding. The OraPAT-IE GAMES trial is supported by a competitive grant funding by the Fondo de Investigaciones Sanitarias, from the National Institute of Health Research, Instituto de Salud Carlos III (ISCIII), Spanish Government (FIS PI19_00861) and by CIBERINFEC (CONSORCIO CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Enfermedades Infecciosas); call for intramural research projects 2024 (file number: IM24/INFEC/1) The protocol of the OraPAT-IE GAMES Trial was approved by the Spanish Medicines and Healthcare Product Regulatory Agency (AEMPS) with the Trial Registration Number EudraCT: 2020-001024-34. ClinicalTrials.gov identifier: NCT05398679. No funding or

sponsorship was received for the publication of this article. J.M. Miro received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–25. M. Hernández-Meneses received a Juan Rodés Research Grant (J23/00035) from the "Instituto de Salud Carlos III" and the "Ministerio de Economia y Competitividad", Madrid (Spain) during 2024-28.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval. The trial will be conducted according to the principles of the last Declaration of Helsinki (accorded by the 64th World Medical Association General Assembly in 2013), the Good Clinical Practice (GCP) and current legislation. The investigator is responsible to guarantee that clinical trial is realized following the directives established by the International Conference on Harmonization about GCP and local legislation. The study was authorized by the Spanish Medicines and Healthcare Products Regulatory Agency (Agencia Española de Medicamentos y Productos Sanitarios / AEMPS) and the Ethic Committee. The trial protocol received the AEMPS approval in December 15th 2021 and the research ethics committee approval in March 8th 2022. A substantial amendment received AEMPs approval and research ethics committee approval in January 25th and February 14th 2023, respectively. The principal investigator or collaborator at each site will provide the Information sheet to the patients and they will explain the study, objectives and clarify any doubt. They will obtain written informed consent from all patients, or their legal representatives (LRs) if they lack capacity, before enrolment. Patients (or their LRs) are free to withdraw from the trial at any time and this will be explicitly stated on the patient's information sheets. Patient personal and clinical information will be managed according to European Regulation 2016/679 and Spanish legislation. Patient's data will be anonymized, identifying every patient by a code. Only the study doctor and collaborators have access to clinical history. Consequently, the patient's identity will not be revealed to any other person, except in cases of medical emergency or if required to do so by law. Access to patient information will be restricted to the study doctor and collaborators, the health authorities (AEMPS), the Clinical Research Ethics Committee, and personnel authorized by the sponsor when they need to check the data and procedures used in the study, but always maintaining the confidentiality of the said information in accordance with current legislation. This protocol has been formulated following the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) statement. This publication follows the Consolidated Standards of Reporting Trials (CONSORT) statement.

Conflict of Interest. Juan Ambrosioni is an Editorial Board member of Infectious Diseases and Therapy. Juan Ambrosioni was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Jose M. Miro is a member of the Reial Academia de Medicina de Catalunya (RAMC), Barcelona, Spain. All named authors declare that they have no competing interests.

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