Full title	A randomized non-inferiority clinical trial of doxycycline vs BPG for early syphilis
Acronym	SY-DOXY SY-BPG
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Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	According to European and US Centers for Disease Control and Prevention (CDC) guidelines, the recommended treatment for uncomplicated early syphilis in adults (i.e. primary, secondary and early latent) is a single intramuscular injection of 2.4 million units of benzathine benzylpenicillin G (BPG). Recent reviews have also recommended BPG as the first-line treatment of early syphilis, reporting a success rate of more than 92% over a large panel of studies. This form of the drug provides weeks of treponemicidal levels of penicillin in the blood, but does not efficiently cross the blood-brain barrier. However, despite the use of BPG for almost 70 years and its status as the gold standard treatment for early syphilis, the need to administer this antibiotic parenterally has led to the use of second-line oral antibiotics, including first-generation macrolides, and then second-generation macrolides, such as azithromycin. Several African studies have shown 1 g azithromycin bid treatment for one day to be effective against early syphilis, but most authors agree that azithromycin should not generally be used as resistance to this macrolide is highly prevalent in Western countries. Moreover, a recent study by our group showed that more than 80% of the treponemal strains isolated in France harbor the mutation conferring resistance to azithromycin. The use of this alternative would, therefore, be highly unlikely to be effective in France. Tetracycline antibiotics have also been proposed as an alternative in patients with a contraindication for BPG or other forms of penicillin. Doxycycline, at a dose of 100 mg orally twice daily for 14 days, has been endorsed as a preferred alternative treatment, but few data are available concerning its efficacy. This issue is crucial, for two main reasons: we have been faced with a recrudescence of early syphilis in most western countries over the last 20 years, increasing the need for BPG, and two periods of

	BPG shortage were experienced in 2013 and 2017, leading to the use of alternative treatments due to the temporary unavailability of BPG or its limitation to cases in which no other treatment was possible. Data for the manufacturing and distribution of antibiotics are not publicly available, but reports of limited availability, shortages, and price increases for old antibiotics suggest that the current system is too fragile to provide what should be a given in modern medicine: access to effective treatment for common and potentially severe bacterial infections. The recurrence of BPG shortages over the last five years has created an urgent need to demonstrate that doxycycline is safe, or at least as safe as BPG, for treating early syphilis. We hypothesize that the recommended doxycycline regimen is not inferior to BPG, and we plan to test this hypothesis in a randomized clinical trial.
Main objective and primary endpoint	The main objective of our study is to show that 100 mg doxycycline bid for 14 days is non-inferior to a single intramuscular injection of 2.4 x 10^6 IU of BPG for the treatment of early syphilis, evaluated as a four-fold decrease in titer in the non-treponemal assay (VDRL or RPR) at month 6 (widely used as the definition of cure in real-life settings). A response will be defined as a four-fold decrease (2 dilutions) in titer in the non-treponemal assay (VDRL or RPR) at month 6 relative to the results of the assay performed before treatment. The two assays (before treatment and at month 6) should be performed in the same laboratory.
Secondary objectives and endpoints	The secondary objectives will be: 1. To evaluate the tolerance of the two regimens in terms of severe adverse events (SAEs) 2. To evaluate adherence to the doxycycline regimen 3. To evaluate the impact of the two regimens on other sexually transmitted diseases at month 6 Secondary endpoints: 1. Occurrence of SAEs in the two groups 2. Adherence to doxycycline, evaluated on the basis of a tablet count between weeks 1 and 2, during planned visits 3. Occurrence of other STDs in the two groups at month 6
Design of the trial	This trial will be an open-label phase III, comparative, randomized study exploring the non-inferiority of doxycycline to the reference medicinal product (benzathine penicillin G) for the treatment of patients with early syphilis, with or without HIV infection. There will be two arms, one treated with the reference medicinal product (BPG) and the other treated with doxycycline. Subjects will be allocated to the two groups at random, in

	a 1:1 ratio.
Population of trial subjects	
Inclusion criteria	- Patients aged ≥ 18 years - Patients who, after the nature of the study has been explained to them, and before any protocol-specific procedures are performed, give informed consent in writing, in accordance with local regulatory requirements - Patients with or without HIV infection in the early stages of syphilis infection according to CDC criteria (primary syphilis, secondary syphilis and early latent syphilis of less than one year's duration), - Patients available for participation and follow-up during the 6 months of the study - Patients covered by the French health insurance system
Exclusion criteria	- Individuals with a history of allergy to one of the two drugs - Individuals with contraindications for either of the study drugs - Individuals with early and late neurosyphilis - Individuals requiring doxycycline treatment - Individuals with late syphilis, whether or not latent (e.g. cutaneous) - Individuals with thrombocytopenia or coagulation disorders contraindicating intramuscular injections - Women who are pregnant or breast-feeding, or of childbearing age not using or planning to use acceptable birth control measures; - Individuals under a measure of legal protection or unable to consent - Individuals participating in any clinical trial with another investigational product in the 28 days preceding the first study visit or intending to participate in another clinical study at any time during the course of this study. - Recent exposure (within the last three months) to either of the two study drugs
Investigational medicinal product(s)	Doxycycline, 100 mg bid, for 14 days
Comparator treatment	Benzathine benzylpencillin G, 2.4 million units administered in a single intramuscular injection
Interventions added for the trial	Sample for DNA detection and sequencing
Risks added by the trial	The trial entails no additional risk
Number of subjects included	85 patients in each group
Number of sites	The trial is a national multicenter trial involving 18 different sites
Duration of the trial	- Inclusion period: 24 months - Participation period (treatment + follow-up): 6 months - *Total duration: 30 months*
Number of enrolments expected per site and per month (per site/per month)	1- CeGIDD Hôtel Dieu, APHP, Prof. Nicolas Dupin - 90/5 2- Service de Dermatologie, Hôpital Henri Mondor,

	APHP, Prof. Olivier Chosidow - 30/2 3- CeGIDD Hôpital Saint-Louis, APHP, Dr Sébastien Fouéré - 90/5 4- Service des MIT, Hôpital Saint-Louis, Prof. Jean-Michel Molina - 20/1-2 5- CeGIDD Hôpital de la Grave, Toulouse, Dr Nathalie Spenatto - 180/10 6- CeGIDD, Lyon, Dr Fatima Yassir Oria - 100/10 7- CeGIDD, Besançon, Dr Fabien Pelletier - 20/1-2 8- CeGIDD, Hôpital Bichat, APHP, Dr Fabrice Bouscarat - 20/1-2 9- Service de Dermatologie, Hôpital de Valenciennes, Dr Annie Vermersch - 100/5 10- CeGIDD, Marseille, Dr Pervenche Martinet - 200/12 11- Service de Dermatologie, Hôpital de la Réunion, Dr Antoine Bertolotti - 50/3 12- Service des MIT, Hôpital de Rennes, Prof. Pierre Tattevin - 40/2 13- Service des MIT, Hôpital de la Pitié-Salpêtrière, APHP, Dr Gentiane Monsel - 90/5 14- CeGIDD, Montpellier, Dr Eric Picot - 90/5 15- Service des MIT, Hôpital de Tourcoing, Dr Isabelle Alcaraz - 100/6 16- CeGIDD CHU de Martinique, Dr André CABIE – 30/1-2 17- Service de Dermatologie, Hôpital de Fréjus, Dr Pascal Del Giudice 18- CH de Pau, Dr Dumondin et Dr Leitao
Statistical analysis	The statistical analyses will be performed by the INSERM CIC 1415 unit and supervised by Bruno Giraudeau. SAS 9.4 and R 3.3 (or further versions) softwares will be used. A detailed analysis plan will be a priori defined. Later modifications must occur before unblinding the database. The statistical analysis will be conducted on both the per-protocol (PP) and intention to treat (ITT) populations as recommended for non-inferiority trials. A statistical report will be written in agreement with the standards as specified in the CONSORT Statement and its extension for non-inferiority trials (http://www.consort-statement.org/).
Sources of funding for the trial	PHRC N 2018
Trial will have a Data Monitoring Committee	No