CLINICAL TRIAL PROTOCOL

"OPEN LABEL AND RANDOMISED CLINICAL TRIAL FOR THE OPTIMIZATION OF THE DURATION OF EMPIRICAL ANTIMICROBIAL THERAPY IN CNACER PATIENTS WITH FEBRILE NEUTROPENIA".

SPONSOR: Fundación Pública Andaluza para la Gestión de la Investigación en Salud se Sevilla (FISEVI)

PROTOCOL CODE: HOWLONG
EudraCT: 2011-005152-34
Version: 5.0 February 2, 2015.

INDEX

1. SUMMARY

1.1. Type of request

Non-comercial, investigator-driven phase IV clinical trial.

1.2. Sponsor

Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI). NIF: G – 41918830.

University Hospital Virgen del Rocío. Ave. Manuel Siurot, s/n. 41013- Seville.

1.3. Official title

Randomized Open Label Clinical Trial Directed to Optimize the Duration of Empirical Antimicrobial Therapy in Hematologic Patients With Febrile Neutropenia.

1.4. Protocol code

HOWLONG, EudraCT: 2011-005152-34.

1.5. Study director

José Miguel Cisneros, PhD. University Hospital Virgen del Rocío, Seville, Spain.

1.6. Paticipating centres

Are detailed in Annex 4.

1.7. Ethics committee

Clinical Research Andalusian Central Ethics Review Committee.

1.8. Responsible for monitoring

Monitor: Fernando Pérez Martínez.

Coordination: Dr. Clara M. Rosso Fernández. Clinical Trial Unit (CTU). University Hospital Virgen del Rocío. General Hospital. Ground floor. Ave. Manuel Siurot, s/n. 41013- Seville.

1.9. Experimental and Control treatments

Experimental Arm: an individualized clinical protocol as the criterion to suspend the empirical antimicrobial therapy (EAT).

- Assigned intervention: EAT discontinuation will occur when the patient is: afebrile, with resolution of signs, symptoms and test abnormalities and normalization of vital signs for ≥ 72 h.

Active Comparator: Control Arm. The recovery of neutropenia (standard) as the criterion to suspend the EAT.

- Assigned intervention: Standard EAT discontinuation. The EAT discontinuation will occur when the neutrophil count is above $0{\cdot}5x10^9$/L and the patient is afebrile, with resolution of signs, symptoms and test abnormalities and normalization of vital signs for >72h.

1.10. Clinical trial phase

Phase IV.

1.11. Objectives

- Primary objective: to establish wether an individualized clinical protocol (ICP) is superior to the standard approach of neutropenia recovery (neutrophil count> 0·5 x10^9/L) for determining EAT discontinuation in a haematological patient with febrile neutropenia (FN).
- Secondary objectives:
    - Demonstrating that ICP is as safe as the standard approach through the comparison of crude mortality (all-cause mortality) and the number of days of fever (fever duration) within 28 days from the start of EAT.
    - Analyse the relationship between procalcitonin (PCT) levels and the appearance of relapsing fever and its potential usefulness as a guide in determining EAT length in haematological patients with FN.

1.12. Design

Prospective, randomised and open clinical trial.

1.13. Condition on study

Febrile neutropenia without etiologic (microbiological) diagnosis, including clinically documented infection or unexplained fever.

- **Definitions**:

Fever: a single temperature determination > 38.5 ° C, or two or more determinations > 38 ° C in the last 12 hours in the absence of another non-infectious cause (transfusion fever among the most common, or pharmacological, such as cytarabine fever).

Neutropenia: neutrophil count < 0·5x10E9/L or < 1.0x10E9/L if a rapid reduction is expected in 24-48 hours.

High-risk neutropenia: expected duration of neutropenia < 0·5x10E9/L during more than 7 days.

1.14. Outcome measures

- **Primary Outcome Measures:** Number of days on which patient is free of antimicrobial treatment [Time Frame: 28 days following the initiation of empiric antibiotic treatment.
- **Secondary Outcome Measures:**
    - Crude mortality [Time Frame: 28 days following the initiation of empiric antibiotic treatment.]
    - Number of days of fever [Time Frame: 28 days following the initiation of empiric antibiotic treatment]
    - The PCT cut-off for predicting recurrent fever.

1.15. Study population and total number of patients

- Adult patients (equal or older than 18 years) of both sexes admitted in the Department of Clinical Hematology who develop a FN. Including fever with unknown source and fever secondary to infection focus of clinical diagnosis without laboratory confirmation.
- The sample size estimated for this study is n=156 patients.

1.16. Treatment duration

The duration of treatment is one of the variables of this study and will depend on the arm to which the patient has been assigned. However the follow-up of patients will be performed for 28 days from the beginning of treatment.

1.17. Schedule and expected study completion date

The total duration of the trial will be more than four years. They include three months for project approvals and coordination, an inclusion period of 48 months, three more months for laboratory determinations, three more for the final analysis of the results and three last months for the publication of the results.

Initial request to the AEMPS: November 2011

Approval date: March 2012

Study start date: April 30, 2012

Study completion date: May 1, 2016

1.18. Investigators

Are detailed in Annex 4.

2. GENERAL INFORMATION

2.1. Trial identification

Protocol code: HOWLONG.

Title: Randomized Open Label Clinical Trial Directed to Optimize the Duration of Empirical Antimicrobial Therapy in Hematologic Patients With Febrile Neutropenia.

2.2. Type of clinical trial

Non-comercial, investigator-driven phase IV clinical trial.

2.3. Description of study products

The investigators of the study will prescribe antimicrobial therapy for FN following the local guidelines of each participating centre. The following antibacterials or a combination of them, among others, will be used: acyclovir, liposomal amphotericin, amikacyn, aztreonam, cefepime, ceftazidime, ganciclovir, imipenem, itraconazole, levofloxacin or ciprofloxacin, meropenem, piperacilin-tazobactam, posaconazole, valacyclovir, valgancyclovir, vancomycin, fluconazole and voriconazole.

The dose, route and and schedule of administration will be done following the technical file of each product.

The duration of therapy will depend on the assignation arm.

2.4. Promotor data

Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI). NIF: G – 41918830.

University Hospital Virgen del Rocío. Ave. Manuel Siurot, s/n. 41013- Seville.

2.5. Principal investigators

Are detailed in Annex 4 .

2.6. Person authorized by the promoter

Dr. Clara M. Rosso Fernández.

2.7. Responsible for monitoring

Monitor: Fernando Pérez Martínez.

Coordination: Dr. Clara M. Rosso Fernández. Clinical Trial Unit (CTU). University Hospital Virgen del Rocío. General Hospital. Ground floor. Ave. Manuel Siurot, s/n. 41013- Seville.

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2.8. Investigators data

Are detailed in Annex 4.

2.9. Setting

Are detailed in Annex 4.

3. RATIONALE

The optimal length of empirical antimicrobial therapy (EAT) in haematological patients with febrile neutropenia (FN) is still unknown. The Infectious Diseases Society of America (IDSA) recommends continuing EAT until neutropenia is recovered up to absolute neutrophil count> 0·5 x10^9/L at least, with questionable scientific evidence [1]. This recommendation may prolong EAT in daily clinical practice. For instance, a patient with fever with no identified source and no microbiological diagnosis will probably receive between two to four weeks of systemic antimicrobial treatment at the onset of neutropenia (median length of 2-3 weeks in high risk patients) even in those patients that remain afebriles and asymptomatics since the second day of treatment. In two large clinical trials involving nearly 2000 haematological patients with NF, the mean length of EAT was 15.8 and 18 days, respectively [2,3]. That length of treatment is superior to the standard approach used for infections considered more serious such as bacteremia and pneumonia and which are treated for a median duration of 7-14 days.

This probable antimicrobial overtreatment sets a strong contrast with the exhortation from the IDSA to the scientific community regarding the urgent need to optimize treatments given the growing increase in resistance and the progressive reduction of active antimicrobials [4]. However, available information on the discontinuation of EAT before recovery from neutropenia is scarce and focuses mainly on pediatric oncology patients with short duration neutropenia. Moreover, the criteria definition for treatment discontinuation is very heterogeneous. Data from a retrospective study including 84 episodes of FN (with a mean of 10 days of neutropenia and 3 days of fever) in pediatric patients. EAT was discontinued before neutropenia recovery in those patients receiving at least 72 hours of intravenous (i.v.) treatment and were afebrile for more than 24 hours. The discontinuation was effective and safe, only two patients experienced recurrence of the fever, there were no re-infections and no deaths or major complications [5].

The recurrence of the fever is one of the risks associated to EAT discontinuation before the recovery of neutropenia. In a pediatric series conducted at the end of the 80s and which included 83 episodes of FN, fever episodes recurred in a total of 21% of patients during the two weeks following discontinuation: all of them were eventually cured. The criterion for discontinuation were: 1) no evidence of infection, 2) baseline cultures negative after 48h and 3) apyrexia for 24h [6]. In a more recent pediatric series of 112 episodes of FN, the frequency of fever recurrence after i.v. therapy discontinuation was 2%. In this study, criterion for treatment discontinuation was at the discretion of the clinician but, in all cases, before recovery from neutropenia [7].

Sequential treatment using oral route antimicrobials after discontinuation of i.v. therapy has been recommended with a C-III level of evidence [1]. A randomized study carried out in low risk pediatric patients demonstrated that it did not reduce the frequency of recurrent fever. This study compared the sequential treatment with cloxacilin plus cefixime *vs*. placebo in 73 children. The criteria for the suspension of i.v. EAT before recovery of neutropenia was apyrexia for more than 24 hours, negative blood culture results at 48 hours, absence of clinical sepsis, cancer in bone marrow remission and absence of comorbid conditions. A total of 9% of patients were readmitted due to fever and neutropenia, 14% of patients in the experimental group *vs.* 6% in the placebo group (p = ns). All of them were cured after restarting the i.v. treatment [8]. In adults, experience in discontinuing EAT before neutropenia recovery is reduced to a pilot study of 10 patients with haematological malignancies and FN who, following five days of apyrexia, were switched off i.v. EAT to oral ciprofloxacin. Fever recurred in three of them [9].

Procalcitonin (PCT) is an indicator for bacterial infection superior than C-reactive protein [10,11]. Levels of PCT used to guide antibacterial treatment reduces the length of treatment duration in patients with respiratory infections and even in patients with serious infections admitted to intensive care units [12–14]. In cancer patients, PCT is useful in the diagnosis of bacteraemia [15]. It has also been studied in FN. PCT values ≥ 0.5 ng/mL at the onset of fever have a negative predictive value of 70% for the diagnosis of bacterial infection [16] and a sensitivity and specificity of 85 and 50%, respectively, in order to distinguish between severe disseminated infection or not [17]. In haematopoietic stem cell transplant recipients with FN and with PCT values ≥ 3 ng/ml, it has been suggested as sign of invasive aspergillosis [18].

PCT values can be elevated by non-infectious causes in cancer patients, treatments with anti-T cell, alemtuzumab, interleukin1 antibodies and polymorphonuclear (PMN) transfusions in graft *versus* host disease (GVHD) [19,20]. Usefulness of PCT in the discontinuation of EAT in FN has not been studied.

The purpose of this study is to determine the effectiveness and safety of an individualized clinical protocol (ICP) to optimize the length of EAT in haematological patients with FN. Additionally, the usefulness of PCT determination as a guide for the discontinuation of EAT in this syndrome is evaluated.

4. STUDY HYPOTHESIS AND OBJECTIVES

4.1. Hypothesis

The hypothesis of the study is that in haematological patients with FN: a) the recovery of neutropenia as a criterion to determine EAT discontinuation unnecessarily prolongs the length of treatment; b) EAT discontinuation guided by an ICP would optimize EAT, reducing its length without negative consequences for the patient; c) PCT might be a useful indicator for the discontinuation of EAT.

4.2. Objectives

The primary objective of the study is to establish whether an ICP is better than the standard approach of neutropenia recovery (neutrophil count> 0·5 $x10^9$/L) for determining EAT discontinuation in a haematological patient with FN.

Secondary objectives include demonstrating that ICP is as safe as the standard approach through the comparison of crude mortality (all-cause mortality) and the number of days of fever (fever duration) within 28 days from the start of EAT. The relationship between PCT levels and the appearance of relapsing fever and its potential usefulness as a guide in determining EAT length in haematological patients with FN is also evaluated.

The outcome definitions and time frames on which they are measured are the following:

Apyrexia	Body temperature measurements < 37.5º C	≥ 72 hours
Clinical recovery	Normal vital signs and resolution of signs and symptoms suggestive of infection	≥ 72 hours
Recovery of neutropenia	Neutrophil count> 0·5 x10^9/L	Up to the end of the follow-up (28 days)
Recurrent fever episodes	New episode of fever after the patient is afebrile > 48h and before neutrophil count> 0·5 x10^9/L	During the follow-up
Number of days free of AT[b] (i.v.)	Result of follow-up days less days administered i.v. AT	On day 28 of follow-up
Number of days free of AT[b] (i.v. + p.o.)	Result of follow-up days less days administered i.v. + p.o. AT	On day 28 of follow-up
Number of days free of fever	Result of follow-up days less days with fever during the entire follow-up	On day 28 of follow-up
Cut-off procalcitonin value	Cut-off value for predicting recurrent fever	At the end of the study
Crude mortality	Death from any cause	On day 28 of follow-up

5. CLINICAL TRIAL DESIGN

5.1. Outcome measures

The primary efficacy endpoint is the number of free-days from antibacterial therapy (EAT). This variable is calculated by the difference between the follow-up days (28 days) and the days of antibacterial treatment administered.

The secondary safety endpoints are: 1) the crude mortality at 28 days from beginning EAT; 2) the number of free-days from fever during follow-up; and 3) the PCT cut-off for predicting recurrent fever. Safety of the interventions will be evaluated by the assessment of any AE occurring from the informed consent form signature up to 28 days after the last dose of the study medication.

5.2. Design and control method

The HOWLONG study (No EudraCT: 2011-005152-34) is a randomised (1:1), controlled, multicentre and open-labelled phase IV clinical trial designed to prove the superiority of an ICP *vs.* the standard approach of neutropenia recovery to decide the discontinuation of EAT. This is a non-commercial investigator-driven clinical study funded through a public competitive call by Instituto de Salud Carlos III, Spanish Ministry of Economy (PI11/02674). The setting for the study will be 6 public and academic hospitals with research group members of the Spanish Network for Research in Infectious Diseases (REIPI) and/or the Spanish Study and/or the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). The study is coordinated by investigators from University Hospital Virgen del Rocío in Seville, Spain. Sponsorship is carried out by Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI) whose scientific responsibilities are delegated to the CTU of the University Hospital Virgen del Rocío, Seville, Spain. Other participating centres are: University Hospital of Bellvitge, University Hospital Clinic and University Hospital Vall d'Hebron (Barcelona, Spain), Hospital de Jerez de la Frontera (Cádiz, Spain) and University Hospital de Salamanca (Salamanca, Spain). The number of participating sites is 6.

5.3. Patients assignments

Adult (18 years of age or older) haematological patients with FN admitted to one of the participating centres are candidates to be included in the study. Eligible patients will be selected from the daily review of results of the complete blood count and temperature curves.

At 72 h (±24) from starting EAT, patients are classified according the clinical and microbiological data available in one of the following diagnoses: a) patient with febrile syndrome with no clinically or microbiologically documented infection; b) patients with fever and clinically documented infection but without etiological

diagnosis and c) patients with FN and etiological diagnosis. Those patients with FN but without etiological diagnoses (infection or others such as GVHD, etc.) that meet all inclusion criteria and no exclusion criteria are eligible for the study.

A 1:1 randomisation procedure assigns the treatment groups: either ICP or standard therapy approach. This randomization is carried out via a list of randomly generated numbers on a computer system using the statistic program Epidat 3.1. The list is held by the CTU whose staff is responsible for communicating the assignment of the study group following verification of the inclusion and exclusion criteria for the study. In order to minimize selection bias, the investigator does not know the study group assigned until the study inform consent is signed by the patient or relative and formal communication to the CTU is complete, even with the open-labelled design.

5.4. Trial treatments description

Haematological patients with neutropenia receive EAT at the onset of fever, following the local guidelines of each participating centre. The following antibacterials or a combination of them, among others, will be used: acyclovir, liposomal amphotericin, amikacyn, aztreonam, cefepime, ceftazidime, ganciclovir, imipenem, itraconazole, levofloxacin or ciprofloxacin, meropenem, piperacilin-tazobactam, posaconazole, valacyclovir, valgancyclovir, vancomycin, fluconazole and voriconazole.

Each patient included will be randomized to one of the following treatment groups:

1- Experimental group (EG): the discontinuation of EAT is carried out when the ICP criteria are met and regardless of the neutrophil count > 0·5 x10^9/L. ICP criteria are: a) apyrexia; b) resolution of signs, symptoms and alterations in complementary tests of the source of infection and c) normal vital signs (blood pressure, heart rate, respiratory rate, O2 saturation and daily diuresis), for ≥ 72 h.

2- Control group (CG): the discontinuation of EAT is carried out when the patient meets ICP criteria and neutrophil count> 0·5 x10^9/L.

The administration of granulocyte colony stimulating factor (G-CSF) will follow the recoomendations of the current protocols of PETHEMA and GELTAMO[1] from the Spanish Society of Hematology and Hemotherapy, based on the current clinical guidelines of the European Organisation for Research and Treatment of Cancer (EORTC)[1] y la National Comprehensive Cancer Network (NCCN)[2]. For this reason the indication and dosage will be the same in both groups.

1 Aapro MS, Bohlius J, Cameron DA, et al. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2011 Jan;47(1):8-32. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours.
2 Crawford J, Althaus B, Armitage J, et al. National Comprehensive Cancer Network (NCCN). Myeloid growth factors. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2007 Feb;5(2):188-202.

Taking into account that all the study drugs are officially approved for EAT in FN in Spain, the sponsor will not provide the study drugs; permission for the use of the drugs through the normal provision of each Pharmacy Hospital has been obtained for every site participating in the study and approved by the Spanish Regulatory Agency (AEMPS: Agencia Española del Medicamento y Productos Sanitarios). In order to ensure the tracking of the products administered, the lot number and expiration dates will be recorded. This is also required by the AEMPS.

There are no absolute contraindications for the use of any other drugs during the study. As such, concomitant medication is permitted in accordance with investigator decision. Contraindications, warnings and precautions for their use and possible interactions with the study drugs are to be taken into account. Only antimicrobial drugs used during the study period will be collected in the study case report form (CRF).

5.5. Randomisation code

The patients will be identified with a three digit code from 001 to 156.

5.6. Study organization

The study coordinating team is formed by the scientific group located in the coordinating site (University Hospital Virgen del Rocío) and the CTU whose personnel are responsible for entire coordination of the study in the sites involved. The CTU personnel will submit administrative authorizations for the study, handle regulatory affairs, provide ethics committee contact and response, take up safety monitoring and pharmacovigilance responsibilities of the sponsor and provide logistical coordination and a contact point for all six participating hospitals.

Data and safety monitoring

The quality of all data collected will be carefully supervised by the CTU. Individuals responsible for the revision and update of data collection will remain in close contact with investigators in order to carry out a close follow-up of study procedures via email or phone contact. Beside this, visits will be organized in order to perform data source verification according to the monitoring plan. All the antibacterial study drugs, as with the rest of concomitant antimicrobial drugs, will be registered in the CRF. An independent, objective review of all accumulated data from the clinical trial is foreseen.

5.7. Identification of data to be registered

The documents that make up the study master file will include what is established in the Standards of Good Clinical Practice (CPMP/ICH/135/95). The researcher will ensure that all persons involved in the study will respect the confidentiality of any

information about the subjects of the trial, as well as the protection of their personal data (according to Law 15/1999, of December 13, Protection of Personal Data).

5.8. Trial completion

The end of the trial will be considered the day of the final visit of the last patient included in the study.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Inclusion criteria

1. Adult (≥18 years) patients of both sex.
2. Admitted to the Haematology ward of any of the participating centres.
3. With any of the following diagnoses: acute leukaemia; lymphoproliferative disease; multiple myeloma; myelodysplastic syndrome; bone marrow aplasia and autologous or allogeneic haematopoietic stem cell transplantation.
4. With high risk FN (expected duration of neutropenia ≤ 0·5x10E9/L more than 7 days) without etiologic (microbiological) diagnosis, including clinically documented infection or unexplained fever.
5. Signed informed consent form
6. Patients who have not previously participated in this trial or, if so, whose final visit took place at least one month before the new inclusion.

6.2. Exclusion criteria

1. Fever with etiological diagnosis including fever due to an infection with microbiological diagnosis and fever with non-infectious aetiologies such as transfusion or drug related, due to graft versus host disease (GVHD) or due to the underlying disease.
2. History of epilepsy.
3. History of tendon disorders related to fluoroquinolone administration.
4. Pregnancy or breastfeeding.
5. Concomitant HIV infection.
6. Severe renal impairment (defined as creatinine clearance below 30 ml/ min).
7. Patients receiving CYP3A4 substrates medication as ergot alkaloids (ergotamine and dihydroergotamine), terfenadine, astemizole, cisapride, pimozide or quinidine, rifampin, carbamazepine, phenobarbital, high doses of ritonavir (400 mg and above, twice daily) St. John's Wort herb.

6.3. Criteria for withdrawal of patients

According to the Declaration of Helsinki, patients have the right to withdraw of the study at any time and for any reason, and may express it personally or through its representative.

- Voluntary abandonment of the patient:
  - By efficiency criteria: When the treatment is ineffective for the patient and can aggravate their illness.
  - By security criteria: When, for whatever reason, the treatment ceases to be safe for the patient. For example, the patient has an

allergic reaction to treatment. Or for any other reason that could jeopardize the life of the patient or have serious consequences for the patient.

- For non-compliance or violation of the rules contained in the protocol: When the patient fails to comply with any of the regulations or test procedures shall be immediately expelled from the test without possibility of accessing it on any other occasion.
- Follow-up of patients withdrawn from the study:
  If a patient is removed prematurely from the trial, the main reason for the suspension will be provided and, as indicated by the PCB rules, the usual procedures for the treatment of the pathology will continue.

- Premature termination of the study:
  Premature termination of the clinical trial may occur by a decision of the regulatory authorities, for a change in the opinion of the Ethics Committee, for safety and/or treatment problems or indications of inefficiency.
  The sponsor reserves the right to interrupt the study in any time for reasonable medical and/or administrative reasons.

7. TREATMENT OF PATIENTS

7.1. Scheduled of visits and assessments

Visit	Selection	0	1	2	3	4*	5†	Final‡
Time	Day of febrile neutropenia onset	72 h (+/-24) of fever onset	72h. Apyrexia	Clinical recovery	Neutrophil count > 0·5 x10^9/L	Recurrent fever	Fever after neutrophil count > 0·5 x10^9/L	+ 28 days
Procedures and tests								
Inclusion/exclusion criteria	X	X						
Informed consent form		X						
Randomisation		X						
Clinical record	X							
Demographic data	X							
Antimicrobial therapy	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X		X
Biochemistry	X	X	X	X	X	X		X
Procalcitonin		X	X	X	X	X		X
Vital signs		X	X	X	X	X		X
Physical examination		X	X	X	X	X		X
Etiological or clinical diagnosis							X	
Concomitant treatment		X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X

7.2. Assessments for visits

Follow-up was organized in four planned visits: visit 1 (72 hours after apyrexia), visit 2 (72 h after clinical recovery), visit 3 (neutrophil count >0·5x10E9/L) and final visit (28±2 days from the beginning of EAT). Additionally, data from unplanned visits were collected with special consideration given to any episode of recurrent fever (visit 4) and any episode of fever or infection following recovery from neutropenia until the end of the follow-up. Additionally, data from unplanned visits will be collected with special consideration given to any episode of recurrent fever (V4) and any episode of fever following recovery from neutropenia.

The visit schedule is planned in order to obtain:

-Inclusion/exclusion criteria

-Consent informed signed

-Randomisation

-Demographic data (age, sex, birthdate, inclusion date)

-Medical history (previous hematopoietic stem cell transplantation, haematological disease, current treatment for main disease)

-Study condition (FN): date of onset of fever, date of onset of neutropenia, probable diagnosis (etiological or clinical diagnosis), clinical presentation including severity signs.

-Clinical status including vital signs and physical examination.

-Biological samples: All the participating sites are asked to process biological samples locally (blood chemistry, blood count and microbiological cultures) at the times described in the visit schedule using standard techniques. Microbiology laboratory departments of each of the participating centres are asked to use the SEIMC Quality Control System [21]. Susceptibility tests are to be interpreted according to European Committee on antimicrobial Susceptibility Testing (EUCAST) version 5.0 (2015) [22] or Clinical Laboratory Standard Institute (CLSI) 2015 recommendations [23].

-Antimicrobial therapy.

-Efficacy and safety variables (including days of EAT administered, days with fever, complete blood count, monitoring of renal and liver function) and adverse events. Data for all the outcome variables will be gathered in the final evaluation (28 days from follow-up).

7.3. Follow-up

Patient´s follow-up will be performed daily by research team members and will be continued until 28 days from the start of antimicrobial therapy.

7.4. Storage, Preservation and Dispensing of Medication

The drugs that will be used in this study will be those that daily are dispensed in the Pharmacy Department of the participating centres. A record of the traceability of the products administered will be included in the study documentation, where active principle, batch of the product and expiration date will be collected.

8. EFFICACY ASSESSMENT

Duration of empirical antimicrobial therapy: only antimicrobials administered intravenously, excluding oral and prescribed antimicrobials with prophylactic indication, will be included.

Efficacy variable: The efficacy end-point is the number or free-days of EAT. This indicator is calculated as the difference between the number of follow-up days (28 days) and the number of days of antibacterial treatment received by each patient.

Fever	Fever: a single temperature determination > 38.5 ° C, or two or more determinations > 38 ° C in the last 12 hours in the absence of another non-infectious cause (transfusion fever among the most common, or pharmacological, such as cytarabine fever)	At febrile neutropenia onset
Recurrent fever episodes	New episode of fever after the patient is afebrile > 48h and before neutrophil count> 0·5 x10^9/L	During the follow-up
Number of days free of EAT (i.v.)	Result of follow-up days less days administered i.v. AT	On day 28 of follow-up
Number of days free of EAT (i.v. + p.o.)	Result of follow-up days less days administered i.v. + p.o. AT	On day 28 of follow-up
Number of days free of fever	Result of follow-up days less days with fever during the entire follow-up	On day 28 of follow-up
Infection episodes	Number and etiology of infections	During the follow-up
Cut-off procalcitonin value	Cut-off value for predicting recurrent fever	At the end of the study
Crude mortality	Death from any cause	On day 28 of follow-up

Procalcitonin samples:

PCT samples are to be taken following the study schedule: 1) at randomization time (V0); 2) following 72h of apyrexia (V1); 3) at clinical recovery (V2); 4) in case of recurrent fever (V4); 5) at neutropenia recovery (V3) and at the end of follow-up (V5). These samples will not be used for the management of patients in the study. These samples are identified by patient code (in order to ensure that association with personal data is not possible) and the visit number for the sample collection. The samples are frozen at -80ºC until the end of the inclusion period, after which PCT determinations will be made. The methodology used in the coordinator centre is ECLIA with the reagents of the commercial house Roche. Thus, if the other centres have the same methodology (technical and reagents), PCT will be determined in its laboratory. Participating centres in which this technique is not available will store the frozen samples and send them to the University Hospital Virgen del Rocío at the end of the inclusion period.

9. SAFETY ASSESSMENT

9.1. Methods for the evaluation of safety

Safety will be assessed in all patients participating in the study, which is by intention to treat (ITT). All adverse events (AE) occurring since the informed consent is signed until the final visit will be collected.

9.2. Definitions

Adverse Event (AE): Is any incidence detrimental to health in a patient or subject of a clinical trial treated with a drug, even if it does not necessarily have a relationship with such treatment. An AE can therefore be any unfavourable sign and unintended (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medication in research, whether or not it is related to the investigational medicinal product.

Adverse reaction (AR): is considered to be any harmful and unintended reaction to a research drug, irrespective of the dose administered. Unlike an AA, in the case of an RA there is a suspicion of a causal relationship between the investigational drug and the AE.

Imputability Criteria: the promoter will classify AA, based on their causal relationship with the drug, according to the Algorithm of Karch and Lasagna (1977), as:

- Definite: There is a reasonable temporal sequence between the administration of drug and the appearance of AA. This event coincides with the AR described for the drug, improves with suppression or reappears after its readministration and cannot be explained by alternative causes.
- Probable: there is a reasonable temporal sequence between the administration of drug and the appearance of AA. This event coincides with the AR described for the drug, improves after discontinuation of treatment and cannot be explained by other alternatives.
- Possible: there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the AR described for the drug but can be explained by alternative causes.
- Conditional or improbable: there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the RAs described for the drug and can be explained by alternative causes.
- Not Related: there is no reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the AR described for the drug and can be explained by alternative causes.

For the purposes of expeditious notification, the categories: definitive, probable and possible of the algorithm of Karch and Lasagna (1977) will be considered as related and the conditional or unlikely category of said algorithm will be considered as unrelated.

The determination of the possible relationship with the treatment of the study is a responsibility of the principal investigator of the research centre or of the person designated by the latter.

Seriousness

Is considered severe any AE or AR that at any dose:

- Cause the death of the patient
- Threatens the life of the patient
- Require hospitalization or prolongation of patient hospitalization
- Cause disability or permanent or major disability
- It results in a congenital anomaly or malformation

For the purposes of notification, suspicions of AA or AR that are considered to be medically important, but not meet the above criteria, including medical events that require intervention to prevent any of the consequences described above, will also be notified as serious. All suspicions of transmission of an infectious agent through a medicine will also be considered serious.

Do not confuse the concept of "serious", described previously, with "severe" that refers to the intensity of AA or AR (mild / moderate / severe).

Serious and Unexpected Adverse Reaction (SUSAR)

Any serious AR whose nature, intensity or consequences do not correspond with the reference information for the drug. In this study, baseline information for the drugs being studied will be the technical file. The unexpected nature of an AR is based on the fact that it has not been observed previously and will not be based on what could be anticipated based on the Pharmacological properties of the medicinal product.

9.3. Adverse events management

9.3.1. Adverse events/pregnancy recording

Crucial data related to the AE are to be included on a specific form provided for the study. In order to collect all the information related to possible AE in the study, each study team will be trained during the site initiation visit on the definitions and rules for communication of an AE. Any AE, whether it is connected to the study medication or not, has to be recorded in the CRF which contains a specific pharmacovigilance section. Serious adverse events must be completed with more detailed information including the event description

(according to international guidelines in pharmacovigilance), date of onset and resolution, severity, assessment of causality to study medication, action taken and other concomitant medication/procedures used for the treatment of the AE. Any AE occurring is monitored using initial and follow-up communication until resolution.

The severe adverse event (SAE) form is centralized in the CTU and its personnel is responsible for reception (by fax or e-mail communication), registration and resolution of queries with participating sites. The identification of any SUSAR is assessed by a safety medical monitor in order to evaluate if information is to be communicated to Regulatory Authorities, Ethics Committees and Investigators following Good Clinical Practice (GPC) rules. In such a case, communication through the EudraVigilance system is foreseen. The safety medical monitor is responsible for any updates in safety information on the investigational medicinal product (IMP).

AA will be collected since the patient signs Informed Consent (CI) up to 28 days after administration of the last dose of the drug in investigation and/or last visit. All AA/pregnancy should be documented in the clinical history of the patient and in the CRF. All AAs should be monitored until their resolution, or at least during the 30 days after discontinuation of study drugs (whatever occurs first), until the toxicity returns to a degree ≤ 1, or until the toxicity is considered irreversible.

In the case of collecting a case of pregnancy information will be collected on:

1. Normal birth, spontaneous or therapeutic abortion (any anomaly congenital detected in the aborted fetus must be documented), dead, congenital anomaly.
2. Neonatal deaths occurring within 30 days of birth.
3. Death of an infant after 30 days if the investigator suspects that he is related to intrauterine exposure to study medication.
4. All infants born after fetal exposure should be followed during the first 12 months after delivery.

Lack of efficacy and overdose should be considered as AA and be collected as such in the CRF.

Any exacerbation of a pre-existing disease occurring after initiation of treatment of the study is also considered as an AA.

Any abnormal results in the laboratory tests that the investigator considers clinically significant and requiring a dose adjustment of the treatment, the transient or permanent interruption of such treatment, or any other type of

intervention or diagnostic evaluation to assess the risk associated with patient, will be collected as AA, and should be investigated and monitored adequately.

9.3.2. Adverse effects due to non-investigational medicinal products

NIMPs are "non-investigational medicinal products (IMPs)" referred in Article 2(d) of Directive 2001/20/EC, which may be provided to patients participating in a clinical trial according to the protocol. For example, some clinical trial protocols require the use of pharmaceutical specialties as concomitant treatments or rescue due to prophylactic, diagnostic or therapeutic reasons and/or for ensure that subjects receive adequate medical care. They may also be used, according to the protocol, to induce a physiological response. These pharmaceutical specialties are not considered research drugs (IMP) according to Directive 2001/20/EC and PCB standards and are classified as "non-investigational medicinal products" (NIMP).

Any AA that may result from the administration of a NIMP should be collected in the CRF. If an SAE is considered to be related only to the NIMP and not relevant to the safety of the study, the investigator is obliged to communicate it, by Yellow Card, to the Pharmacovigilance Centre.

Procedure for notification of SAE/pregnancies

In the event of an SAE or a pregnancy case is collected, a member of the investigating team will complete and sign the notification form and will send it, by fax, immediately and always within 24 hours after having knowledge of the event to:

Fax: 0034 954232992

The CTU staff will review the form received and, if necessary, will request additional information from the investigator. When additional information is obtained, or it is resolved or unlikely to change, a follow-up report must be completed and faxed to the CTU. If there is a suspicion of a SUSAR, the investigator must provide the follow-up information requested by the CTU.

Any SAE occurring more than 30 days after the end of treatment (without a time limit) should be reported if the investigator considers AAG to be related to the study treatment (i.e, if it is a serious adverse reaction) or if it is medically important.

It is not necessary to notify the CTU of the following SAE:

- Hospitalization or death due to the progression of haematological disease.
- Hospitalization for the performance of scheduled tests.
- Hospitalization to administer the study drug or to provide palliative care, terminal care or to perform scheduled surgical interventions.

- Hospitalization or prolongation of hospitalization to perform a procedure required by the protocol.
- Hospitalization or prolongation of hospitalization as a part of the routine procedure of the centre (for example, removal of a stent after surgery)

They will be collected in the CRF and in the patient's medical history.

Expedited notification of SUSARS to Health Authorities

The CTU will be responsible for notifying all the SUSARS collected in the study to the AEMPS, to the CEICs and to the Health Authorities, following the procedure indicated in the current legislation.

9.3.3. Notification deadlines

The maximum period for notification of an individual SUSAR suspect case shall be 15 calendar days from the date on which the promoter has had knowledge of it. When SUSAR is suspected of causing death the patient, or endangered his life, the promoter will send the information within 7 calendar days from the date on which he/she become aware of it.

9.3.4. Expedited notification of any other relevant safety information

The CTU will also notify, in an expeditious manner, all information that could modify the benefit/risk balance of the investigational medicinal product, or determine changes in the administration schedule or in the performance of the trial.

9.3.5. Annual safety reports

Safety annual reports are issued with all the safety information in the study being reported to regulatory Authorities and Ethics Committees.

9.3.6. Notification to investigators

The CTU will communicate to the investigators any safety information that may affect the safety of the trial subjects as soon as possible. The SUSAR information will be sent annually, in an aggregated form, in a list along with a brief analysis of the data provided. Throughout the study, the investigator will also be informed of any safety aspects that impact the conduct of the clinical trial or product development, including interruption of the development program or modifications to the protocol related to safety.

9.4. **Discontinuation of study drugs due to adverse events**.

Certain events or conditions may necessitate temporary or permanent discontinuation of study medication. Patients presenting such events or conditions will remain in the study and will be followed until completion. Any patient who interrupts the study medication should temporarily restart it as soon as possible. Study procedures will be discontinued and will be replaced by out-of-study

procedures with continuing the follow-up of patients. If the administered drug is permanently discontinued, subsequent therapy is left to the discretion of the investigator.

Temporary discontinuation

Criteria for temporary discontinuation of study drugs: The development of a toxicity that, depending on its nature and severity, requires a temporary discontinuation of study medication until the toxicity is resolved, as well as the development of another medical condition that would discourage the administration of study drug. The decision to temporarily interrupt study medication in this situation will be left to the discretion of the investigator. The period during which patient is not taking the study medication will be as short as possible.

Permanent discontinuation

Criteria for permanent discontinuation of study drugs: Toxicity development requiring permanent discontinuation of any study drug, patient refusal to continue treatment, when in the opinion of the investigator continuing study therapy is not the best option for the patient and completion of the study.

10. STATISTICAL ANALYSES

10.1. Statistical methods

This clinical trial is designed to demonstrate the superiority of ICP over the standard approach in the decision to discontinue EAT. Safety evaluation of is included in a non-inferiority assumption. Efficacy analysis will be performed in the entire clinically evaluable population (CEP): patients who have completed EAT following the study group assigned without protocol deviation during follow-up. The clinical and microbiologically evaluable population (CMEP) is defined as the clinically evaluable population in which non-infectious diseases of any aetiology were suspected or diagnosed and no other antimicrobials than those indicated for the FN episode were started during follow-up. The safety analysis will be performed by intention to treat (ITT) in all randomized patients.

The most favourable PCT cut-off level for predicting recurrent fever will be determined through analyses of sensitivity, specificity and receiver operating characteristic (ROC) curves.

A descriptive analysis expressing qualitative variables as proportions and quantitative variables as median and interquartile range (RIC) or mean (SD). (depending on if they follow a normal distribution or not) will be performed. In order to compare study groups, the Chi squared test or Fisher's exact test for qualitative variables and *t* Student's test or Mann-Whitney *U*, when necessary, in quantitative variables will be used.

Analysis will be performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago III, U.S.A.) v 19.0.

An interim analysis is planned once 50% of patients will be recruited.

10.2. Sample size

The sample size estimated for this study is n=156 patients. For analysis efficacy, designed to determine whether ICP is superior to the standard approach for optimizing the length of EAT, the number of EAT free-days is assessed.

The sample size calculation was performed on the basis of a 90% statistical power to detect differences in the contrast of null hypothesis H_0: the mean difference is equal to the superiority limit, through a T-Student unilateral test (superiority) for two independent samples, with a significance level of 5% and assuming that the superiority limit is 3 days, a mean EAT free-day number of 12 days in the CG and of 18 days in the EG [2], a standard deviation (SD) of 6 days in both groups and a proportion of experimental patients of 50% of the total. It will be necessary to include 70 patients in the EG and 70 patients in the CG, making a total of 140

patients. Taking into account that the expected percentage of patients to withdraw from the study will be 10%, it is necessary to recruit 78 patients in each group, making a total of 156 patients in the study.

11. ETHICAL CONSIDERATIONS

HOWLONG will be carried out in accordance with the Declaration of Helsinki principles and the legal norm directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use. Moreover, all local applicable rules such as Spanish Royal Degree 223/2004 will be considered for development of the study.

Due to the pragmatic design of the study, similarities to clinical practice mean that special ethical considerations are more present than those that are typical for the development of a randomized trial. It is not ethical but practical aspects of this study which make its organization complex since the intervention itself is not the classical administration of a drug, but the comparison of criteria for withdrawal.

The trial will start after obtaining approval from a Central Ethics Review Committee, conformity from the Directors of the Institutions, and the authorization of the AEMPS and the local ethic committees at each site participating in the trial. A formal contract agreement was signed between each institution and the sponsor of the study.

11.1. Informed consent

The subject of the trial will grant his/she consent after having understood, through a previous interview with the investigator, the objectives of the trial, risks and drawbacks, as well as the conditions under which it will be carried out, and after being informed of their right to withdraw from the trial in any time without causing any harm.

Each study candidate patient will be provided with the corresponding informed consent in which the purposes of the research will be explained in addition to the procedures to be used, the expected duration of the research and the expected benefits to the patient and others.

Finally, each patient will be informed of the intention of publishing the results of the study in a scientific publication. To include a patient in the trial, he/she must give his or her informed consent to all assumptions.

Consent will be documented through an information sheet for the subject (Annex 1) and the consent form (Annex 2 and 3).

When the subject of the trial is unable to giving consent:

- If the subject is an adult without the capacity to give informed consent, the investigator will obtain the consent of the legal representative, having been informed about the possible risks, discomforts and benefits of the trial. The

consent shall reflect the alleged wish of the subject and may be withdrawn at any time without detriment to him. When the conditions of the subject allows it, he/she shall also give its consent to participate in the trial, after having received all the relevant information adapted to their level of understanding. In this case, the investigator shall take into account the wish of the person unable to withdraw from the trial.

- When the subject is not able to make decisions due to physical or psychic state and has no legal representative, consent will be provided by individuals linked to him for family or de facto reasons. The subject participating in a clinical trial, or their legal representative, may revoke their consent at any time, without further explanation and without detriment to him.

11.2. Protection of data

The confidentiality of records which could identify subjects in the HOWLONG study will be protected in accordance with the EU Directive 2001/20/EC. All laws on the control and protection of personal information will be carefully followed. The identity of patients will not be disclosed in the CRF; names will be replaced by an alphanumeric code and any material related to the trial such as samples will be identified in the same way so that any personal information can be revealed.

11.3. Acquisition and dispensing study medication

The process of obtaining the medicines will be the usual for the hospital setting. We deal with section 30 of the Clarification document on the application of the regulation of clinical trials with medicinal products for their use in human of May 1, 2004 (version no. 6, May 2008)

Thus, given the non-commercial nature of this study and the characteristics of the same, in that the study medication is the same that is usually used, the drugs will be in charge of the participating centres.

11.4. Monitoring and audit

The study will be monitored through local visits, telephone calls and periodic inspection of CRF with sufficient frequency to check the following:

- Rate of inclusion of patients, compliance with the rules of the protocol procedures, data integrity and accuracy, verification with original documents and occurrence of EA.
- Monitoring visits will be performed by the study monitor. It is understood that she/he may access the medical records of the patients after requesting the researcher, who will facilitate access to the documentation to authorized persons.

The study may be audited by an independent organism. Equally, members of the local clinical trials Committees of the participating centres may carry out "follow-up visits" to it.

11.5. Non-compliance

Non-compliance with the protocol and/or regulatory requirements from an investigator or from the staff members of the promotor should lead to rapid intervention by the promotor, to ensure compliance.

If the monitoring and / or audit identify a serious and / or persistent non-compliance on the part of an investigator, the promoter must remove the investigator of the study. When the investigator is withdrawn due to noncompliance, it must promptly notify to the regulatory authorities.

11.6. Premature discontinuation

If the trial ends prematurely or is suspended, the sponsor must inform authorities of the completion or suspension and of the reason for it as specified by the regulatory requirements.

12. FOUNDING SOURCE AND INSURANCE

12.1. Funding source

The study has obtained funding by a public Call for Projects Grants of Health Research in 2011, promoted by Subdirección General de Evaluación y Fomento de la Investigación of Instituto de Salud Carlos III, Spanish Ministry of Economy (PI11/02674).

12.2. Insurance

The study´s sponsor, FISEVI has an insurance policy with the company HDI, policy number 30/002/001692 (directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 and Royal Decree 223/2004, of February 6, 2004) which will provide compensation for impairment of your health or injury occurring in connection with the participation in the study.

13. PUBLICATION POLICY

13.1. Publishing policy

The publishing policy will be in accordance with the provisions of Royal Decree 223/2004 of February 6, which regulates the Clinical Trials with medicines, article 38, which includes the next text:

1. The sponsor is obliged to publish both positive and negative results from authorized clinical trials in scientific journals.
2. The funds and sources of funding obtained will be recorded.
3. The anonymity of the subjects participating in the program shall be maintained
4. The results or conclusions of the clinical trials shall be communicated preferably in scientific publications before being made available to the public. The effivacy of procedures not yet determined or exaggerated will not be spread prematurely.
5. Advertising of products undergoing clinical research is absolutely prohibited, as set forth in Law 34/1998, of November 11, General of Advertising.

SPIRIT 2013 Explanation and Elaboration paper and SPIRIT statement [24–26] will be followed for the reporting of results to any scientific journal or event.

13.2. Amendments to the protocol

To ensure the study conditions and the valid statistical analysis of the data, neither the researcher nor the developer can alter the conditions of the agreed upon and stipulated in this protocol. Any modification to the protocol which may have an impact on the conduct of the study or potential benefit for the patient, or which may affect patient safety, including changes in study objectives, study design, patient population, sample size, study procedures or significant administrative aspects, would require a formal amendment to the protocol. The study coordination team and the CTU will agree such an amendment. The amendment will then become an integral part of the study protocol. In case the amendments require the approval of the ethical committees and/or Authorities, it will be necessary to obtain it.

13.3. Documentation

Whether the study is completed or terminated prematurely, the promoter must ensure that clinical study reports are prepared and provided to the Authorities.

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ANNEX 1: PATIENTS INFORMATION SHEET

STUDY TITLE: Open label and randomised clinical trial for the optimization of the duration of empirical antimicrobial therapy in cancer patients with febrile neutropenia.
TRIAL CODE: HOWLONG (EudraCT: 2011-005152-34)
PROMOTER: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI)

INTRODUCTION

We are writing to you to inform you of a research study in which you are invited to participate. The study was approved by the corresponding Clinical Research Andalusian Central Ethics Review Committee and the Spanish Agency of Medicines and Health Products (AEMPS) in accordance with current legislation (Royal Decree 223/2004) regulating clinical trials with medication.
It is our intention to provide you with correct and sufficient information so that you may evaluate and judge whether or not to participate in this study.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary and you will have the right to withdraw your consent at any time with no consequences for your future treatment nor any effect on your relationship with your doctor or your level of care. Additionally, your doctor will have the option of cancelling your participation if he/she believes this is advisable, taking into account your clinical evolution. The necessary conditions for this are described in the study.

GENERAL STUDY DESCRIPTION

You have a haematological disease and currently suffer from a complication called febrile neutropenia, which may be severe. Febrile neutropenia consist in fever and a decrease in the number of neutrophils, a type of white blood cells that defend us from infections, usually caused by the treatment with chemotherapy. When it is diagnosed, some tests such as blood cultures and the indication of antimicrobial therapy are necessary. This treatment is maintained until fever disappears and recovery from neutropenia is achieved. Neutropenia usually lasts between two and three weeks and, as such, the duration of antibacterial therapy is frequently prolonged and longer than the standard duration of 7-10 days employed when treating other serious infections.

SCOPE OF THE STUDY

The aim of the study is to improve antibacterial treatment for febrile neutropenia, optimizing its duration. Waiting until neutrophil recovery to withdraw antibacterial treatment has the risk of unnecessarily prolonging the duration of antibacterial therapy with the consequence of exposure to the adverse effects of these drugs and the potential emergence of resistant bacterial infections.

In order to avoid receiving more antibiotics than necessary, in this study we will administer antibacterial treatment to patients with febrile neutropenia until fever and symptoms and signs of infection have disappeared, regardless of the neutrophil count.

Regarding to the safety of this study, you will be clinically evaluated daily and the diagnostic tests that you would need would be performed.

Moreover, we will assess the usefulness of procalcitonin (a protein determined by means of a blood test) to decide upon antibacterial therapy withdrawal.

STUDY DESIGN

There are two treatment groups. Patients from both groups will be treated according the hospital's guidelines and using the available antibacterials.

For patients included in the EG, the antibacterial treatment will be withdrawn when patient is afebrile and signs and symptoms of infections (such as cough, abdominal pain, diarrhea…) are resolved and vital signs are normal (blood pressure, heart rate, respiratory rate, etc.) for at least 72 hours.

For patients included in the CG, the antibacterial treatment will be withdrawn when patient is afebrile and signs and symptoms of infections (such as cough, abdominal pain, diarrhea…) are resolved and vital signs are normal (blood pressure, heart rate, respiratory rate, etc.) for at least 72 hours and neutrophil count exceeds $0{\cdot}5x10^9$/L.

Group allocation is carried out using "randomisation". The probability of belonging to one group or another is equal. However, the doctor will always know which group you belong to. If you participate in the study, the duration will be 28 days.

We will carry out all routine test while you are admitted, the following being carried out daily:

-Vital signs measurements

-Physical examination

-Laboratory test: blood count, biochemistry

Other test performed less frequently during admission:

-Blood cultures

-Chest X-ray

-Other microbiological cultures when necessary

In addition, for the purpose of this study, 6 additional blood samples will be taken (a total of 60 ml of blood).

BENEFITS AND RISK OF YOUR PARTICIPATION IN THE STUDY

If our hypothesis is correct, this trial will improve the antibacterial treatment of patients who, like you, have fever and neutropenia, avoiding unnecessary prolonged antibacterial therapies and subsequent adverse effects and infections due to resistant bacteria. Participating in this study may not provide you with any health benefits but the results may be useful for futures patients who have febrile neutropenia such as you have now.

All the drugs used in this study have been approved by the Spanish Regulatory Agency (AEMPS) and are property commercialized. Given the different infections contemplated in this study, depending on the patient and the bacteria causing the infection, one of the following antibacterials or a combination of them will be used: acyclovir, liposomal amphotericin, amikacyn, aztreonam, cefepime, ceftazidime, ganciclovir, imipenem, itraconazole, levofloxacin or ciprofloxacin, meropenem, piperacilin-tazobactam, posaconazole, valacyclovir, valgancyclovir, vancomycin, fluconazole and voriconazole.

Most of these antibiotics have adverse effects, some of which can be life-threatening. The adverse affects you may suffer as a result of the administration of these drugs include, among others: digestive upset, rash, allergy reactions, muscle pain, blood and hepato-biliary disorders, ototoxicity, kidney problems (including renal failure), and neurological disorders. However, the risk of suffering from any of these adverse effects as a result of your participation in this study is not higher than if receiving the currently established treatment for febrile neutropenia.

All adverse effects or undesirable events occurring during the study will be monitored and registered and, as such, we request you to inform your study doctor if you have any discomfort or experience any other new issue.

ALTERNATIVE TREATMENTS

There are other effective alternatives currently available for the treatment of your illness and which you may receive if you do not participate in this study. Therefore, if you do not wish to participate, the research team will treat you with an alternative empirical antimicrobial therapy.

INSURANCE

In compliance with the law, this study´s sponsor has an insurance policy with the company HDI, policy number 30/002/001692 (directive 2001/20/EC of the European

Parliament and the Council of 4 April 2001 and Royal Decree 223/2004, of February 6, 2004) which will provide compensation for impairment of your health or injury occurring in connection with your participation in the study.

CONFIDENTIALITY

The treatment, communication and transfer of personal data from all participating subjects shall comply with the provisions of Law 15/1999, of December 13 on the Protection of Personal data, and Royal Decree 1720/2007 of December 21, approving the Regulations implementing this law. According to the provisions of that legislation, you may exercise your rights of access, rectification, opposition and cancellation of data. Such request should be addressed to your study doctor. The data collected for the study will be identified using a single code and only your study doctor/collaborators have the code in order to correlate these data with your and your clinical records. Therefore, your identity will not be disclosed to any person with exceptions, such as in case of medical emergencies or by legal requirement. Access yo your personal information is restricted to the study doctor/collaborators, Health Autothorities (AEMPS), the Ethics Committee for Clinical Research and persons authorized by the sponsor when they need to check the data and study procedures, but always maintaining the confidentiality of such data in accordance wiht current legislation.

Data from this study will be used only for the specific purposes of the study.

OTHER RELEVANT INFORMATION

Any new information concerning the drugs used in the study found during your participation and which could affect your willingness to participate or continue in the study will be notified by your study doctor as soon as possible.

You may abandon the study at any time without further explanation. If you decide to withdraw your consent to participate in this study, no new data will be added to the database and you may request the destruction of all previously retained identifiable samples in order to avoid the implimentation of new analyses.

You should be made aware thta you may be excluded from the study is the promoter, study investigators, health autothorities or AE event related to the study medication or if they consider that you are not accomplishing the procedures required for the study. In either case, you will receive an adequate explanation of the reasons leading to your removal from the study.

By signing the attached consent form, you agree to comply with the study procedures which have been explanied to you. When the participation is complete, you will receive

the best treatment available and which your doctor considers the most appropiate for your condition.

The head of the study in your hospital is Dr _____ (telephone number_____). He/she will be available for any questions or calirification you may need regarding your participation in the study. If you agree, please sign the attached consent form. A copy of the signed informed consent is for you.

ANNEX 2. WRITTEN PATIENT INFORMED CONSENT

Open label and randomised clinical trial for the optimization of the duration of empirical antimicrobial therapy in cancer patients with febrile neutropenia.

Trial code: HOWLONG (EudraCT: 2011-005152-34)

Promoter: Fundación Pública Andaluza para la Gestión de la Investigación en Salud se Sevilla (FISEVI)

I (name and surname)_____

DECLARE THAT

I have read the information leaflet provided by the medical team

I have had the opportunity to express my questions and doubts

I have received appropiate answers to my questions

I have received sufficient information on the study

I HAVE SPOKEN WITH_____

(name of the researcher)

I understand that my participation is voluntary

I understand that I can pull out of the study

1. Whenever I want
2. Without having to give explanations
3. Without this affecting my medical care

THEREFORE, I freely give my conformity:

- To participate in this study.

- To provide additional confidential information required for the control and quality guarantee of the study by personnel assigned by the sponsor and competent authorities or, if applicable, the Ethics Committee.

- To archive the encoded information within the framework of data confidentiality.

Name of the person that gives his/her informed consent_____

Signature of the person that gives his/her informed consent_____Date (dd/mm/yy)

Numer or the researcher_____

Researcher signature_____Date (dd/mm/yy)

ANNEX 3: LEGAL SURROGATES WRITTEN INFORMED CONSENT FORM

LEGAL SURROGATES INFORMED CONSENT

Open label and randomised clinical trial for the optimization of the duration of empirical antimicrobial therapy in cancer patients with febrile neutropenia.

Trial code: HOWLONG (EudraCT: 2011-005152-34)

Promoter: Fundación Pública Andaluza para la Gestión de la Investigación en Salud se Sevilla (FISEVI)

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I HAVE SPOKEN WITH_____

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- To archive the encoded information within the framework of data confidentiality.

Name of the person that gives his/her informed consent_____

Signature of the person that gives his/her informed consent_____Date (dd/mm/yy)

Numer or the researcher_____

Researcher signature_____Date (dd/mm/yy)

ANNEX 4. INVESTIGATORS AND PARTICIPATING CENTRES

Number	Centre	City	Investigators
Centres from the beginning of the study, protocol version 1.1			
1	University Hospital Virgen del Rocío, Institute of Biomedicine of Seville	Seville	PI: Dr. José Miguel Cisneros Herreros Collaborators: Dr. Ildefonso Espigado Dra. Rocío Parody Dr. José González-Campos Dr. José Falantes Dª. María Rosario López Dra. Manuela Aguilar-Guisado Dr. José Molin Dra. Clara Mª Rosso-Fernández Lda. Inmaculada Domínguez-Pascual Dra. Almudena Martín-Peña Dra. María Isabel Montero
Extension to other centres, protocol version 2.0			
2	University Hospital of Salamanca	Salamanca	PI: Lourdes Vázquez-López Collaborators: Dra. Lucía López Corral Dra. Mª Dolores Caballero Barrigón
3	University Hospital Vall d´Hebron-Universitat Autònoma,	Barcelona	IP: Dr. Pere Barba-Suñol Collaborators: Dra. Isabel Ruiz Dra. Nerea Castillo Flores Dr. David Valcárcel
4	University Hospital Clinic	Barcelona	IP: Dra. Montserrat Rovira Tarrats
Extension to other centres, protocol version 4.1			
5	Hospital of Jerez de la Frontera	Jerez de la Frontera	PI: Dr. Sebastián Garzón López Collaborators: Dr. Eusebio Martín-Chacon Dr. Vicente Rubio-Sánchez Dra. Mª. Dolores Madrigal-Toscano
Extension to other centre, protocol version 5.0			
6	University Hospital of Bellvitge-Institute of Oncology of Catalonia (ICO)	Barcelona	PI: Dra. Carlota Gudiol Collaborators: Dra. Carolina García-Vidal Dra. Cristina Royo-Cebrecos Dña. Cristina Padilla-Montero

PI: principal investigator