Tittle of the clinical investigation: "A randomized phase-III trial assessing lenalidomide and dexamethasome with or without clarithromycine as initial treatment for multiple myeloma in patients ineligible for an autologous transplant"

Protocol code: GEM-CLARIDEX

EudraCT identification number:2015-001183-19

Final report–20/02/2024

Drug under study: Lenalidomide, Dexamethasome, Clarithromycine

Clinical trial phase: III

Sponsor:

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Main study coordinator in Spain: ***Dr. Mª Victoria Mateos Manteca***

Main study coordinator in the United States: ***Dr. Ruben Niesvizky***

Study authorization date: 30/09/2015
Study completion date: 31/10/2023

This clinical trial was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Research Involving Human Subjects and Good Clinical Practice in the Conduct of Clinical Trials Involving Human Subjects.

Contents

ABBREVIATED TERMS AND DEFINITIONS

AE	Adverse events
ANC	Absolute Neutrophil Count
CI	Confidence intervals
CR	Complete remission
CT	Computed tomography
DDR	Duration of response
EFS	Event-free survival
EC	Ethical committee
FACIT	Functional Assessment Scale for Chronic Illness Treatment Fatigue
HR	Hazard ratio
IC	Informed consent
ICH GCP	International Council for Harmonisation Good Clinical Practice
IMWG	International myeloma working group
ITT	Intention to treat (population)
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PFS2	Second episode of disease progression
PR	Partial response
RDI	Relative dose intensity

RI	Renal insuffiency
SAE	Serious adverse event
SGOT/AST	Serum glutamic oxaloacetic transaminase
SGPT/ALT	Serum glutame pyruvate transaminase
TTP	Time to progression
VGPR	Very good partial response

1. Ethics

1.1. Ethical committees

This study has been evaluated by all local or corresponding ethical committees (ECs) for each participating centres. The Clinical Research Ethics Committee of the Navarra Hospitalacted as the main CE for the single approval opinion.

1.2. Study conduct

This study was conducted in accordance with the Spanish legislation in force (Real Decreto 223/20004) and in accordance with the ethical principles set forth on the Declaration of Helsinki as well as the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines.

1.3. The inform consent form

The informed consent (IC) was obtained from all patients during the first assessment evaluation. The written IC explained benefits, risks, study procedures, and study aims using a plain, understandable language. Participation in the clinical was completely voluntary, and patients withdraw consent at any time during the trial without prejudice regarding future medical treatment.

2. Sponsor, principal investigators, and clinical research organization

2.1. Sponsor

Name: Fundación Programa Español de Tratamientos en Hematología (PETHEMA).
Address: C/ Santa Balbina, 2, Oficinas 3-4-5
28023 ARAVACA (Madrid)

Fax: +34 916266232

Authorized person to sign the clinical trial protocol:

Name: Dr. Juan José Lahuerta

2.2. Principal investigators and participating centres

Principal coordinating investigator in Spain:
Name: Dr. Mª Victoria Mateos Manteca
Hospital Universitario de Salamanca, Salamanca.

Principal coordinating investigator in the United States:
Name: Dr. Ruben Niesviykz

Hospital Presbiteriano de Nueva York/Centro Médico Weill Cornell, Nueva York.

Principal investigaros and participating sites:
The list of centers participating in the clinical trial is attached in the corresponding Appendiix.

2.3. Clinical Research Organization

Name: CABYC

Address: Avenida Somosierra, 12; 28703San Sebastián de los Reyes, Madrid (España)

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3. Clinical investigation plan

This clinical trial was a multicenter, open-label, randomized, phase III study designed to assess lenalidomide and dexamethasome, with and without clarithromycin, as an initial treatment for patients with newly diagnosed multiple myeloma (MM) ineligible for autologous transplantation and newly treated.

3.1. Purpose of the clinical investigation

Multiple Myeloma is an incurable disease, mainly because of its recurrence after transient control. The main goal of the treatment in newly diagnosed MM patients ineligible for transplant is to prolonge an initial disease-free interval before relapse and improve their quality of life[1].

The gold standard treatment for newly diagnosed MM patients who are ineligible for transplant is the administration of lenalidomide in combination with dexamethasome as continuous therapy. After the publication of the results of FIRST[2,3], a phase-III clinical study including 1623 patientscomparing the effects of a continuous treatment with lenalidomideand dexamethasome (Rd treatment) versus the effects of administering Rd followed by melphalan, presdnisone y thalidomidefor a duration of 18 cycles each. Theprogression-free survival (PFS) and overall survival (OS) of the patients who received Rd continuously were longer than those who were administered Rd for a limited period of time followed by melphalan, prednisone and thalidomide. In addition, the treatment was well tolerated by all patients and there was no sign of developing second primary malignancies[3].

Based on the immunomodulatory properties of clarithromycin and its effects on increasing serum corticosteroid life, new studies were performed including this drug. These studies revealed that clarithromycin had a synergistic effect with the anitmyeloma and antiangiogenic

activity of thalidomide and dexamethasome[4,5]. In a phase-II clinical trial, the addition of clarithromycin combined with thalidomide and dexamethasome improved the response in newly diagnosed and relapsed/refractory MM patients. Among 40 patients, five (13%) showed complete remission (defined by complete disappearance of the monoclonal component) and the rates of complete, partial, and minor responses were 40%, 13%, and 27%, respectively.

To improve our understanding of clarithromycin effects in MM patients, the GEM/PETHEMA group conducted a phase-II study where patients received 500mg of clarithromycin twice daily, 25mg daily of lenalidomide for 21 days of a 28-day cycle, and a 40mg dose of dexamethasome per week (BiRd treatment). This treatment achieved an overall response rate of 90.3%, and a response rate of 30%. A retrospective case-matched analysis comparing patients treated with BiRd versus Rd showed that adding clarithromycin to Rd significantly increased patients'response rates, from 79.1% to 90.3% of patients achieving partial response (PR) or greater, and from 13.9% to 45.8% vs of patients achieving complete remission. To confirm the superiority of BiRd treatment compared to Rd in terms of response and survival rates, the present phase III randomized open-label study was proposed. In this study, we compared the efficacy of Rd vs BiRd treatment in newly diagnosed, transplant-ineligible MM patients in terms of their response and survival rates. We hypothesized that the addition of clarithromycin would lead to a higher response rate, shorter time to response, and lower toxicity than treatment based solely on lenalidomide and dexamethasome.

In patients with renal insufficiency (RI) at the time of diagnosis, the lenalidomide dose was adjusted according to RI degreeof the patients. Lenalidomide is administered orally, rapidly absorbed and eliminated mainly by renal excretion. In patients with RI, the clearance rate of this compound is lower, which results in an increaseddrug concentration in the blood stream and, in turn, a prolonged half-life fo the drug potentially enhancing the immunosuppression experienced by these patients. As for clarithromycine in RI patients, only those patients whose erythrocyte filtration rate was less than 30 received a halved drug dose, since clarithromycine is eliminated mainly (70%) by the liver. In these patients, the daily dose was reduced to 500mg.

1 Kyle, R. A. Long-term survival in multiple myeloma. *N Engl J Med***308**, 314-316 (1983). https://doi.org:10.1056/nejm198302103080604

2 Weber, D. M. *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med***357**, 2133-2142 (2007). https://doi.org:10.1056/NEJMoa070596

3 Benboubker, L. *et al.* Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med***371**, 906-917 (2014). https://doi.org:10.1056/NEJMoa1402551

4 Fost, D. A. *et al.* Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol***103**, 1031-1035 (1999). https://doi.org:10.1016/s0091-6749(99)70175-2

5 Coleman, M. *et al.* BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma***43**, 1777-1782 (2002). https://doi.org:10.1080/1042819021000006303

3.2. Clinical study objectives

3.2.1. Primary objectives

The primary objective of this study was to compare the efficacy of the BiRd treatments vs the Rd treatment.

3.2.2. Secondary objectives

The secondary objectives of this study were:

- To evaluate the efficacy of the combination of clarithromycin, lenalidomide (Revlimid®) and dexamethasome (BiRd), compared to lenalidomide and dexamethasome (Rd) alone, as induction therapy for patients with newly diagnosed MM, ineligible for transplantation and without prior MM treatment
- To compare the Overall Response Rate (ORR) of BiRd vs. Rd
- To determine and compare: duration of response (DDR), event-free survival (EFS), time to progression (TTP), and OS of BiRd vs Rd
- To Evaluate safety and toxicity in each treatment arm
- To evaluate and compare the minimal residual disease after BiRd treatment compared to that after Rd treatment
- To determine and compare the efficacy of BiRd vs. Rd from baseline to the second episode of disease progression (PFS2)
- To evaluate, determine and compare the quality of life of the patients receiving BiRd from those receiving Rd

3.3. Clinical investigation endpoints

Primary endpoint:

- Progression-free survival, which was defined as the time from random inclusion in one of the treatments to the onset of disease progression or death

Secondary endpoints:

- Response rate, defined according to (IMWG) criteria
- Event-free survival, with an event define as the termination of patient's participation in the study for any reason, including disease progression, lack of response to treatment, intolerance to medication or death
- Overall survival (OS)

- DDR
- PFS2
- Quality of life measured by the Functional Assessment Scale for Chronic Illness Treatment-Fatigue (FACIT Fatigue Scale), as part of a quality of life questionnaire
- Toxicity of both treatment regimens as defined in CTCAE V4.0

3.4. Inclusion and exclusion criteria

Inclusion criteria:

- Ability to understand the content of the IC form and willigness to sign the IC form
- Age of 65 years or older at the time of signing the IC form
- The patient was diagnosed with MM and had not been previously treated. The diagnosis of MM was made according to the following definition: presence of ≥ 10% clonal plasma cells in bone marrow or bone or extramedullary plasmacytoma evidenced by biopsy, and one or more of the defining events of myeloma:
    - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, in particular:
      -Hypercalcemia: serum calcium > 0.25mmol/L (> 1mg/dL) above the upper limit of normal, or > 2.75mmol/L (> 11mg/dL)
      -RI: creatinine clearance < 40mL per minute, or serum creatinine > 177µmol/L (> 2mg/dL)
      -Anemia: hemoglobin > 20g/L below the lower limit of normal, or hemoglobin < 100g/L
      -Bone lesions: one or more osteolytic lesions as observed on radiography, computed tomography (CT) or PET-CT scan
    - One or more of the following biomarkers of malignancy:
      -Percentage of clonal plasma cells in bone marrow ≥ 60%.
      -Ratio between serum free light chains involved and not involved ≥ 100
      - > 1 focal lesion on whole body or spine and pelvis based on magnetic resonance imaging (MRI)
- The patient should not have received anti-myeloma treatment in the 14 days prior to the start of study treatment except for corticosteroids with a maximum allowable dose equivalent to three pulses of dexamethasome (40 mg daily for 4 days, which equals one pulse)

- Patients may have previously received adjuvant antiresorptive therapy (i.e., pamidronate or zoledronic acid) as standard treatment, or radiation therapy as palliative treatment for pain and/or spinal cord compression
- Patient had measurable disease defined by > 0.5 g/dL of serum monoclonal protein, > 10 mg/dL of serum free light chains involved (either kappa or lambda), provided the serum free light chain ratio is abnormal, urinary excretion of M protein > 0.2g /24 hours and/or measurable plasmacytoma(s) of at least 1cm in greatest dimension measured by either CT scan or MRI
- Patient had a Karnofsky Functional Status ≥ 60% (> 50% if due to myeloma bone involvement)
- The patient could receive anticoagulants prophylactically, as detailed in section 9.1 of the protocol (patients intolerant to aspirin may use warfarin, acenocoumarol or low molecular weight heparin)
- If the patient was a woman with gestational capacity, she should have had a negative serum or urine pregnancy test, with a sensitivity of at least 25mlUI/mL performed within the previous 10-14 days, and again during the 24hours prior to starting the lenalidomide treatment. She had to agree to either abstain from heterosexual intercourse or to geing using at least TWO methods of birth control, one highly effective and one additional effective method AT THE SAME TIME, at least 28 days prior to starting the treatment. The woman with gestational capacity had also to consent to pregnancy testing during treatment. Maleds had to agree to use latex condoms during sexual contact with women with gestational capacity even if they had undergone a successful vasectomy.
- The patient had a life expectancy ≥ 3 months
- Patients had to meet the following laboratory parameters:
    - Absolute Neutrophil Count (ANC)≥ 1.0 x 109/L
    - Hemoglobine ≥ 7 g/dL
    - Platelet count ≥ 75,000/mm3 (> 30 x 109/L if there is extensive bone marrow infiltration)
    - Serum SGOT/AST< 3.0 x upper limit of normality
    - Serum SGPT/ALT < 3.0 x LSN
    - Serum total bilirubin < 2.0 mg/dL (34 µmol/L)

Exclusion criteria:

- Patient with non-measurable MM (not measurable monoclonal protein or free light chains in blood or urine, or non-measurable plasmacytoma on radiological examination)

- Patient with a history of previous neoplasms. Exceptions were those patients who had been disease-free for ≥ 5 years prior to study enrolment. Exceptions were basal cell or squamous cell carcinoma of the skin, the cervix or breast in situ carcinoma, or localized prostate cancer with a Gleason score < 7, with stable prostate-specific antigen levels
- The patient had experienced a myocardial infarction during the 6 months prior to enrolment in the study, or a NYHA class III or IV heart failure, ejection fraction <35%, uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, evidence of prolonged QTC interval on pretreatment electrocardiogram, or active conduction system abnormalities
- The patient was a pregnant or breastfeeding woman
- The patient was infected with the human immunodeficiency virus
- The patient presented an ongoing B or C hepatitis infection.
- The patient presented ongoing bacterial or viral infections, or any coexisting medical condition that would significantly put them at a higher risk when administrating the treatment
- The patient was unable to take oral medications in a realiably fashion
- The patient was previously diagnosed with hypersensitivity to dexamethasome, clarithromycin, lenalidomide, or thalidomide
- The patient had a history of thromboembolic events in the last 4 weeks prior to the date of study enrolment
- The patient presented medical or psychiatric disorders, which according to principal investigator's assessment, could interfere with his/her compliance of the protocol or ability to give IC
- The patient had been previously treated for MM
- The patient presented symptomatic AL amyloidosis, either primary (isolated) orsecondary (in patients diagnosed with MM)

3.5. Amendments

Amendment n. 1 of December 1, 2015

This amendment made to the original clinical investigation plan updated the participating centers and their corresponding principal investigators of this stduy. The Clínica de la Universidad de Navarra as well as Dr. Paula Rodríguez Oterowere replaced by the Complejo Hospitalario de Navarra and Dr. Jose María Arguiñano Pérez, who acted as the new Principal Investigator.

Amendment n. 2 of July 20, 2016

The sponsor of this study modified the clinical investigation plan as well as the patient's IC form:

Amendment of the clinical investigation plan

The list of participating centers and corresponding investigators was updated with this amendment, replacing Dr. Eduardo Ríos Herranz from the Hospital Virgen de Valme by Dr. María del Carmen Couto Caro as the new Principal Investigator.

Additionally, the exclusion criteria were expanded, including the following text: "Patients with symptomatic AL amyloidosis, both primary (isolated) and secondary (in MM-adiagnosed patients)". Section 9.3.1 on treatments is also modified in the protocol. Specifically, a daily tablet of SeptimForte® is deleted as a prophylaxis for *Pneumocystis carinii*driven-Pneumonia starting during the cycle 2 of either BiRd or Rd therapy. Regarding the follow-up of cases that achieve strict complete response, the text is modified to perform a quantification of free light chains in serum and from 24-hour urine every three months. Additionally, the Appendix regarding proposals for biological studies is modified, adding 10cc of SERUM (in GELOSA) to study the soluble components of the immune system, both in samples taken at the time of diagnosis and in the second, ninth and eighteenth follow-up cycles.

Amendment of the IC form

The amendment made to the original IC form (IC form approved by the corresponding CEs, version 1, May 26, 2015) deleted information regarding the risks associated with lenalidomide, the drug under assessment during the clinical study. It also updated the risks associated to this drug administration for women and pregnancy, especially for those who were are advised against taking birth control pills and/or hormone replacement therapy. The centres where all the study samples were extracted and processed for the biobank and subsequent related genetic studies were also included with the current amendment of the IC form.

All the above mentioned modifications were included in the IC form, version 2, July 15, 2015.

Finally, this amendment changed the original clinical investigator plan, upadating the Researcher's Manual (versions 19 and 20).

<u>Amendment n. 3 of January 2, 2017</u>

The amendment of clinical investigation plan included a higher number of abbreviations and modifies the study design. The previously established criteria for the treatment of RI patients with regard to the lenalidomide dose. The section describing the purpose of the study is expanded including the impact of RI on lanlidomide and clarithromycine intake and the measures that will be carried out to adjust the dose in patients with RI.

The inclusion criteria related to creatinine clearance rate were modified by this amendment. The seventh and eighth sections of the clinical investigation plan related to therapeutic agents, their toxicity, and side effects were also modified. The impact of RI on the pharmacokinetic parameters of lenalidomide as well as the increased side effects of this drug in IR patients were also included in this version of the clinical investigation plan. Finally, the therapeutic plan (treatment and dose modification) of the clinical investigation plan was changed to adjust the lenalidomide and clarithromycin doses. It was also included a chart with the recommended lenalidomide doses for MM patients based on their grade of RI. A slight modification on the grading and reporting of adverse events (AE) as well as larger version of the bibliography are included in this version of the clinical investigation plan. Appendix I is also modified, adjusting the biochemical parameters that define the response criteria and stable or plateau disease. In the same section, one of the parameters defining progressive disease is slightly altered. This amendment also modifies Appendix X, which specifies proposals for biological studies, adding peripheral blood and serum in gelose to this appendix.

All these modifications are reflected on the Clinical Investigation Plan, version 5, January 2, 207.

Amendment n. 4 of January 15, 2018

This amendment changed the clinical investigation plant (version 5 of January 2, 2017) by including additional participating centres with their corresponding principal investigators. In particular, the following centres were added:

- Hospital General Universitario Gregorio Marañón: Cristina Encínas
- Hospital Clínico de Valencia: Anabel Teruel
- Hospital Universitario Central de Asturias: Ángel Ramírez Payer
- Hospital Insular Las Palmas de Gran Canaria: José David González San Miguel
- Hospital Vírgen de la Arrixaca: Valentín Cabañas Perianes
- Hospital de Txagorritxu: Ernesto Pérez Persona
- Hospital Universitario Marqués de Valdecilla: Arancha Bermúdez
- Hospital de Galdakao: Jose Enrique de la Puerta
- Hospital del SAS de Jerez: Sebastián Garzón López
- Complejo Hospitalario Universitario A Coruña (CHUAC): Ana María Vale López

As a potential back-up participating centre, the Complejo Hospitalario Universitario de Gran Canaria Doctor Negrín with Dr. Alexia Suarez Cabrera was also included. Sponsor's point of contact information was also updated.

In addition, the study design of the clinical investigation plan as well as the number of patients were modified, adjusting in both cases the number of patients planned to be recruited in the United States: from the initial 153 patients planned to be included, these were reduced to 55. In contrast, the number of patients planned to be included in Spain was increased from 153 to 285. The planned date for completion of the study and the planned time for recruitment were also modified, increasing from 2-3 years to 4-5 years and from 2 years to 3.5 years, respectively. The statistical considerations to determine the sample size base on the estimate recruitment rate were also slightly modified, leading to an increase of 340 patients over 3.5 years.

All these modifications were included in the Clinical Investigation Plan, version 5, of January 15, 2018.

<u>Amendment n. 5 of May, 30, 2018</u>

This amendment included changes in the previous clinical investigation plan and IC form.

Amendment of the Clinical Investigation PLan

This amendment changed the previous clinical investigation plan by updating the participating clinical sites. In particular, the following modifications were included:

- The Hospital Universitario Central de Asturias with Ángel Ramírez Payer is replaced by the Hospital de Povisa withCésar Soto as Principal Investigator
- The Hospital Insular Las Palmas de Gran Canaria with Jose David González San Miguel is replaced by Hospital Virgen de la Concha with Roberto Hernández as Principal Investigator.
- The Hospital de Galdakao with Jose Enrique de la Puerta is replaced by Hospital del Henares with Juan Francisco del Campo as Principal Investigator
- The Principal Investigator of the Hospital Universitario Marqués de Valdecilla, Arancha Bermúdez is replaced by Guillermo Martín Sánchez

Moreover, the premature termination of the study section was slightly modified, with 'Celgene' being eliminated and only 'research team or the Monitoring Committee' remaining as evaluators of the toxicity grade. Celgene's role was also modified in the sections of the clinical investigation plan related to the Safety Data Monitoring Committee. The telephone number of the point of contact the central laboratory, where samples should be sent, was modified. Finally, a number of grammatical errors found in the text were corrected.

Amendments of the IC form

The text related to the risks associated with lenalidomide was modified to use a more accessible language for the patients. The side effects description and their frequency, including the parameters by which the frequency is determined, were also modified: very frequent (the probability of occurrence is equal to or greater than 10%), frequent (the probability of occurrence is between 1% and less than 10%), and infrequent (the probability of occurrence is between 0.1% and less than 1%). In addition, "Reported post-marketing risks of lenalidomide" was modified and the possible effect of lenalidomide on driving and use of machines was added. The text concerning "New cancers" was also modified.

These modifications were included in the IC form, version 4 of January 15, 2018.

Amendment n. 6 of May, 30, 2018

The changes introduced by this amendment referred to the lenalidomide supplier (i.e. Almac Clinical Services from Ireland), due to the situation caused by BREXIT. After the authorization received from the Spanish Medicines Agency, the updated versions of the clinical investigation plan (version 6, dated May 30, 2018) and of the IC form (version 5, dated May 30, 2018) were generated.

Amendment n. 7 of October 16, 2020

This amendment modified the clinical investigation plan (version 7, of May 30, 2018) and the IC form.

Amendments of the clinical investigation plan

Dr. Juan José Lahuerta Palacios was replaced by Dr. Joaquín Martínez López as principal investigator of the Hospital 12 de octubre. This modification was included in the Clinical Investigation Plan version 8 dated of October 16, 2020.

Amendments of the IC form

This modification updated the biosafety associated with lenalidomide, one of the drugs under study in this clinical trial. It included risks whose occurrence is determined to be "very rare", i.e., risks whose probability of occurrence is between 0.01% and less than 0.10%. All these changes were consolidated in version 6 of the IC form, dated October 16, 2020.

Amendment n. 8 of July 22, 2022

The previous version of the clinical investigation plan was modified to introduce the following changes in terms of principal investigators of the corresponding participating sites:

- Hospital Virgen del Rocío: Dr. Jesús Martínez Sánchez is replaced by Dr. Marta Reinoso Segura as the new Principal Investigator

- Hospital Universitario Virgen de las Nieves: Dr. Rafael Ríos Tamayo is stepping down as Principal Investigator and is replaced by Dr. Esther Clavero Sánchez
- Centro Dr. Peset: Dr. Javier de la Rubia Comos is replaced by Dr. María de la Paz Ribas García as Principal Investigator
- Hospital de Tzagorritxu: Dr. Ernesto Pérez Persona is replaced by Dr. Buenaventura Buendía Ureña as Principal Investigator.

All these modifications were included in the Clinical Investigation plan, version 9 of July 22, 2022.

3.6. Clinical investigation design and study objectives

This clinical study was a multicenter, open-label, randomized, phase III study designed to assess efficacy and safety of lenalidomide and dexamethasome, with and without clarithromycin, in patients with newly diagnosed multiple myeloma (MM) who were ineligibles for autologous transplantation. Eligible patients were randomized in a 1:1 ratio to be treated with either clarithromycin, lenalidomide and low-dose dexamethasome (BiRd arm), or lenalidomide and low-dose dexamethasome (Rd arm).

Patients in **the BiRd arm** were treated with lenalidomide, dexamethasome, and clarithromycin until disease progression or unacceptable toxicity (Figure 1). In each cycle, which lasted 28 days, patients received a 25mg dose of lenalidomide administered orally from day one to day 21, followed by a seven-day rest period (days 22-28). They were also orally adminesterd a dose of 25mg clarithromycin daily. Once a week, patients received a 40 mg dose of dexamethasome orally (days 1, 8, 15 and 22 of each cycle).

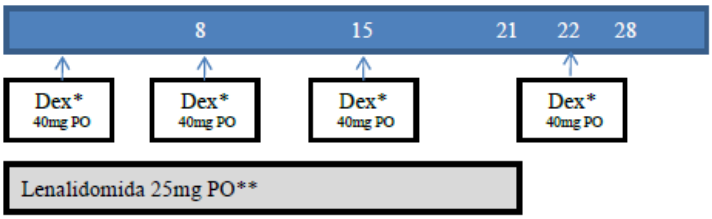

Figure1. Schematic representation displaying the medical treatment received by the patients of the BiRd arm. The day of the cycle is represented in the blue bar.

Patients in **the Rd arm** were treated with lenalidomide and dexamethasome until disease progression or unacceptable toxicity (Figure 2). The regimen and mode of administration of both drugs was identical to that established for patients in the BiRd regimen.

In RI patients from both arms, the lenalidomide dose was adjusted to the RI grade of each patient. Similarly, patients older than 75 years old were treated with a dexamethasome dose of 20mg regardless of the type of regimen to which they had been assigned.

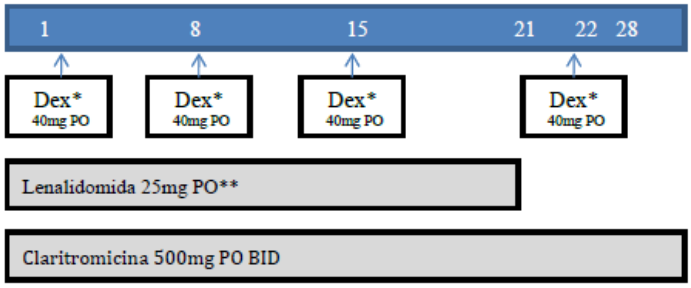

Figure 2. Schematic representation displaying the medical treatment received by the patients of the Rd arm.

All patients were followed up to determine the treatment response rate, toxicity, OS, EFS, and PFS. Urine and blood samples were collected every 28 days (at the beginning of each cycle) to analyze the presence of monoclonal proteins and serum free light chain concentration. The reporting of patient's EMR and immune status was performed either by flow cytometry or PCR according to the procedures described in AppendixX of the clinical investigation plan. Similarly, the relative dose intensity (RDI) was calculated for each patient according to the criteria established in the clinical investigation plan. Quality of life was assessed by means of questionnaires including the FACIT Fatigue Scale.

The toxicity analysis was based on adverse events (AEs). Those were evaluated according to the fourth version of the NCI CTCAE. In case toxicity had precluded treatment with one of the study medications, the treatment was continued with the remaining assigned medications. Patients who were unable to receive all drugs in the assigned treatment arm were withdrawn from the study.

3.7. Statistical analysis

A total estimate of 340 patients (285 in Spain and 55 in the United States) were planned to be recruited for this clinical study over approximately four and a half years and assuming a dropout rate of 10%. This number of patients was calculated using as a reference the PFS results of the FIRST clinical trial, in which it was observed that patients who received Rd treatment had a PFS of approximately 25.5 months. To achieve a statistical power of 90% to detect a 75% increase in median PFS (44.6 vs. 25.5 months) and a bilateral significance of 0.05, the sample population size was 286 patients.

The **intention-to-treat (ITT) patient population** included all registered patients who underwent randomization whereas the safety population comprised patients who received any dose of treatment trial. Continous variables were analysed with descriptive statistics, and categorical variables were summarized in frequency tables.

Analysis of the **primary endpoint, (i.e. PFS)** for each treatment group was performed on the ITT population using Kaplan-Meier survival analysis, with 95% confidence intervals (CI) calculated using Greenwood tests. **Comparison of PFS** between the two treatment arms was performed using a log-rank testand the treatment effect (hazard ratio [HR] and correspong 95% CI) was determined by using a stratified Cox regression model, with treatment as the only explanatory variable. Other time-to-event end points were calculated similarly.

Analysis of **secondary endpoints** included comparison of partially response rates and **complete response rates**. Binary endpoints were assessed with with Fisher exact tes and an odds ratio and two-sided 95% CI were calculatd. The **toxicity analysis** was performed including all identified AEs and the frequency of patients experiencing each AE was estimated. The **safety analysis** was carried out including all patients who received at least one dose of the drugs under study.

3.8. Results

3.8.1. Population demographics

Between December 2015 and December 2018, a total of 286 patients with newly diagnosed MM, ineligible for transplantation, were recruited. These patients were randomized to the BiRd treatment arm (143 patients) or the Rd treatment arm (143 patients).

The mean characteristics of the population are described in the following table:

Characteristic	**Rd group (n=143)**	**BiRd group (n=143)**
Mean age (interval), years	75 (65-91)	76 (65-93)
Age distribution (interval), %		
<75 years	65 (45.5)	59 (41.3)
≥75 years	78 (54.5)	84 (58.7)
Sex, n, %		
Male	71 (49.7)	64 (44.8)
Female	72 (50.3)	79 (55.2)
ECOG performance status, n, (%)		
0	36 (25.9)	41 (29.3)
1	68 (48.9)	66 (47.1)
2	33 (23.7)	29 (20.7)

ISS disease stage, n, (%) I II III	 36 (25.1) 53 (37.0) 54 (37.7)	 33 (23.0) 59 (41.2) 51 (35.6)
R-ISS disease stage, n, (%) I II III	 15 (12.8) 79 (67.5) 23 (19.6)	 17 (14.4) 83 (70.3) 18 (15.2)
Type of measurable disease, n, (%) IgG IgA Bence Jones	 74 (52.1) 47 (33) 21 (14.7)	 84 (58.7) 37 (25.8) 17 (11.8)
Cytogenetic profile, n/total, (%) Standard risk High risk	 106/131 (80.9) 25/131 (19.1)	 108/130 (83.1) 22/130 (16.9)

ECOG: Eastern Cooperative Oncology Group, whose scale reflects the degree of disability of patients from 0 to 5, with increasing values corresponding to a higher degree of inability to perform daily living functions; ISS: International Staging System (ISS), a scale used to measure the stage of the disease and is obtained from the combination of serum levels of ß2-microglobulins and albumin. The three stages are defined by: I (ß2-microglobulins <3.5 mg/L and albumin=3.5 g/dL), II (values between stage I and stage III), and III (ß2-microglobulin =5.5 mg/L). The higher the stage, the more advanced the disease. The R-ISS scale is derived from the combination of ISS, chromosomal abnormalities (CA) detected by interphase fluorescence in situ hybridization after purification of CD138 plasma cells and serum lactate dehydrogenase (LDH) levels. R-ISS stage I includes ISS stage I, no elevated risk of CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal normal LDH levels (values less than the maximum established for normal values); R-ISS stage III is defined by ISS stage III with elevated risk of CA or elevated LDH levels; R=ISS stage II includes the remaining possible combinations.The risk of cytogenetic abnormalities was measured based on CD138 fluorescence in situ hybridization of bone marrow samples obtained at the time of diagnosis. High risk was defined by the presence of at least one of the following abnormalities: del17p, t(4;14), or t(14;16).

Among all enrolled patients, 135 (94%) of the BiRd group and 140 (98%) of the Rd group completed at least one cycle of the scheduled treatment. The mean duration of treatment was 15 months (range 0.2-44 months) for the BiRd group, with a mean number of 10 cycles (range 1-48 cycles). The corresponding values for the Rd group were 15.9 months (0.4-46 months) and a mean number of 14 cycles (range 1-47). As of February 7, 2020, 108 patients (75.5%) in the BiRd group and 82 patients (57.3%) in the Rd group had discontinued their participation in the study, with disease progression being the main cause for treatment termination in both groups.

3.8.2. Efficacy

Efficacy analysis on the ITT population revealed that, at 19 months (0-54 months, interval) from the start of treatment, a total of 132 patients died or showed disease progression. The percentage of patients alive with no signs of disease progression at 19-month follow-up was

53.4% (95% CI, 44.5-62.2) and 61.9% (95% CI, 53.5-70.3) in the BiRd and Rd groups, respectively. No significant differences were found between the mean PFS of the two groups (Figure 3), with a HR of disease progression or death of 1.293 (95% CI, 0.919-1.818, p = 0.14) for patients in the BiRd group compared with those in the Rd.

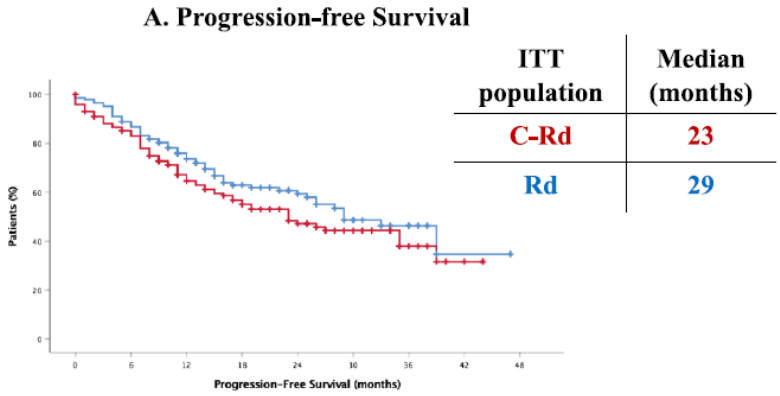

Figure 3. Prgoression-free survival of all patients from the ITT population.

Subgroup analysis of patients based on age showed that, in patients older or 75 years of age, the mean PFS of the BiRd group was lower than that of those in the Rd group (19 vs 28 months, respectively; p=0.05). However, this trend disappeared when the analysis was performed in patients younger than 75 years, with PFS being comparable for both arms (NR vs 33 months; p=ns) (Figure 4).

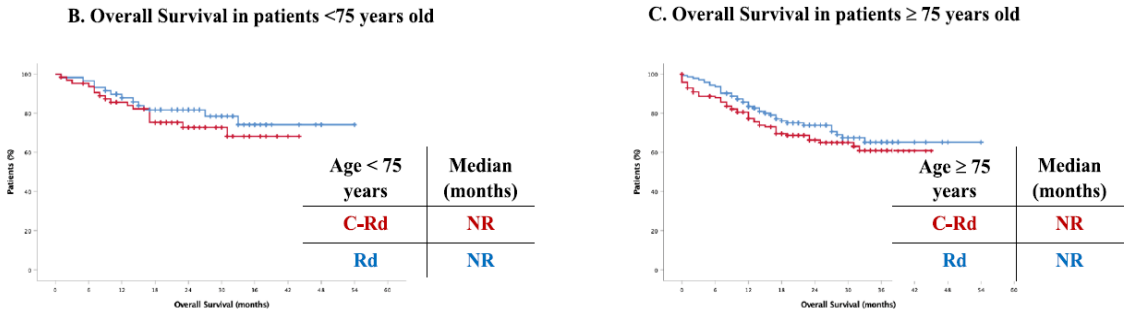

Figure 4. PFS in patients <75 years old and in patients s ≥75 years old.

The mean TTP at 39 months of follow-up in the ITT population was 39 months in both arms (p=0.962). Among patients <75 years old who had been assigned to the Rd group, the mean TTP was 39 months, whereas in those in the BiRd group, this was not reached (p=0.601). However, in patients ≥75 years old in the BiRd group, the mean TTP was 35 months, and this was not reached in the Rd group (p=0.559).

The percentage of patients with complete remission (CR) was higher in the BiRd arm compared withthe Rd arm (22.6% vs. 14.4%, p=0.048). Among the 29 patients who achieved CR and in

whom minimal residual disease (MRD) grade was assessed, no significant differences were detected between the two groups (4/15 [27%] patients in the BiRd group vs 5/14 [36%] patients in the Rd group, p=ns). No significant differences were found between both arms in the percentage of patients who showed very good partial response (VPR) or better: 52.9% in the BiRd group vs 46.1% in the Rd group.

The ORR of the ITT population was 71.5% and 76.4% patients in the BiRd and Rd arms, respectively. The following table shows the OR and the different response categories observed in both groups.

Type of response rate	**BiRd group (n=143)**	**Rd group (n=143)**	***P***
Overall response, n (%)	71.5%	76.4%	
≥ Complete response or better	33 (23%)	21 (14%)	0.048
Stringent complete response	31(22%)	18(12%)	0.029
Complete response	2 (1%)	3 (2%)	0.144
Very good partial response or better	77 (53%)	67 (46%)	0.500
Very good partial response	44 (30%)	46 (32%)	0.449
Partial response	27 (19%)	44 (31%)	0.014
Stable disease	27 (19%)	31 (21%)	0.330
Progressive disease	1 (0.6%)	1 (0.6%)	0.750
Response could not be evaluated	0 (3%)	3 (2%)	0.124

Response types were evaluated according to IMWG (International Myeloma Working Group) instructions.

The mean time to first response was 28 days in both gorups, and the mean time to CR in patients receiving BiRd and Rd treatment was 5.5 and 5.4 months, respectively. At 19 months of follow-up, 84 patients had died: 46 patients in the BiRd group and 38 patients in the Rd group, equivalent respectively to 32.1% and 26.5% of the total number of patients in each group. Overall survival had not been achieved in either cohort at this time (Figure 5).

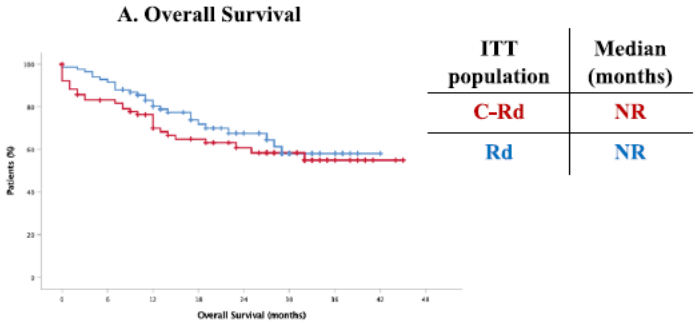

Figure 5. PFS analysis in patients<75 years and ≥75 years old.

3.8.3. Safety analysis

In the following table, data on the safety profile in BiRd or Rd patients according to age is presented. Information related AEs for all grades is displayed in the bottom part of the table, whereas the lower part contains only grade 3 and 4 AEs.

	All patients			**Patients ≤ 75 years**			**Patients> 75 years**		
AE or SPM, n, %	BiRd (n=143)	Rd (n=143)	*P*	BiRd (n=143)	Rd (n=143)	*P*	BiRd (n=143)	Rd (n=143)	*P*
Hematologic									
Neutropenia	34 (24)	51(36)	0.038	15(23)	14(24)	1	19(24)	37(44)	0.013
Anemia	26 (18)	28(20)	0.080	7 (14)	8 (14)	0.784	19 (24)	20 (24)	1
Thrombocytopenia	21 (15)	22 (15)	1	9 (14)	7 (12)	0.794	12 (15)	15 (18)	0.833
Nonhematologic									
Asthenia	40 (28)	44 (31)	0.697	17 (26)	12 (20)	0.526	23 (29)	32 (38)	0.319
Steroid-related	58 (41)	40 (28)	0.034	28 (34)	17 (29)	0.134	30 (38)	23 (27)	0.180

Infections	78 (55)	76 (53)	0.906	32 (49)	28 (47)	0.859	46 (59)	48 (57)	0.874
Pneumonia	11 (8)	19 (13)	0.176	6 (9)	7 (12)	0.771	5 (6)	6 (7)	0.748
Thrombosis and pulmonary embolism	9 (6)	11 (8)	0.817	5 (8)	5 (8)	1	4 (5)	6 (7)	0.748
Diarrhea	22 (15)	24 (17)	0.872	10 (15)	10 (17)	1	12 (15)	14 (17)	0.834
Invasive second primary cancer	4 (3)	1 (1)	0.371	1 (1)	0 (0)	1	3 (4)	1 (1)	0.353

Most common adverse events (AE) and second primary malignancies (SPM) reported over the treatment in the safety population.

Tabla 4	**All patients**			**Patients ≤ 75 years**			**Patients> 75 years**		
AE or SPM, n, %	BiRd (n=143)	Rd (n=143)	*P*	BiRd (n=143)	Rd (n=143)	*P*	BiRd (n=143)	Rd (n=143)	*P*
Hematologic									
Neutropenia	17 (12)	28 (19)	0.104	6 (9)	7 (12)	0.771	11 (14)	21 (25)	0.114
Anemia	4 (3)	10 (7)	0.169	1 (2)	5 (8)	0.101	3 (4)	5 (6)	0.721
Thrombocytopenia	7 (5)	4 (3)	0.541	2 (3)	1 (2)	1	5 (6)	3 (3)	0.483
Nonhematologic									
Asthenia	16 (11)	4 (3)	0.009	5 (8)	1 (2)	0.211	11 (14)	3 (3)	0.024
Steroid-related	22 (15)	9 (6)	0.021	7 (11)	5 (8)	0.766	15 (19)	5 (6)	0.006
Infecctions	43 (30)	36 (25)	0.428	17 (26)	15 (25)	1	26 (33)	21 (25)	0.299
Pneumonia	10 (7)	14 (10)	0.523	6 (9)	6 (10)	1	4 (5)	8 (9)	0.373
Thrombosis and pulmonary embolism	2 (1)	6 (14)	0.282	0 (0)	4 (7)	0.049	2 (2)	2 (2)	1
Diarhrea	4 (3)	5 (3)	1	2 (3)	2 (3)	1	2 (2)	3 (3)	1
Invasive second primary cancer	4 (3)	1 (1)	0.371	1 (1)	0 (0)	1	3 (4)	1 (1)	0.353

Most common adverse events (AE) of grade 3-4 and second primary malignancies (SPM) reported over the treatment in the safety population.

The most frequent grade three and four AEs observed in all patients were neutropenia (with frequencies of 12% and 19% in the BiRd and Rd group, respectively, p=ns), asthenia (11% vs 3%, p=0.009), and steroid-related (15% vs 6%, p=0.021). Steroid-related AEs included cases of tremor, anxiety, insomnia, nervousness, hyperglycemia, confusion, cataracts, skin rashes, and aphonia. The incidence of infections was similar between both groups, with 30% of all patients in the BiRd group and 25% of all patients in the Rd group developing infections, p=ns.

Age subgroup anaylsis of the toxicity associated with each treatment showed that among patients ≤ 75 years of age, grade 3-4 AEs were equally frequent in both arms. However, in patients >75 years old, the rates of asthenia (14% vs 3%, p=0.024), steroid-related AEs (19% vs 5%, p=0.006) and infections (33% vs 25%, p=ns) were higher in the BiRd group than in the Rd group.

Among patients in the BiRd group, 55.9% suffered at least one serious adverse event (SAE), while among patients in the Rd group, the percentage was 47.6%. The most frequently reported type of SAE in both groups was infections: 24% of patients in the BiRd group and 28% of patients in the Rd group reported at least one infection during the course of the study. Overall, 25% of patients in the BiRd group and 19.5% of patients in the Rd group discontinued treatment prematurely due to AEs, with one patients in each group due to an infection.

Over the course of this study, a total of 90 deaths were documented: 50 in the BiRd group and 40 in the Rd group, with a similar rate of deaths due to disease progression; 14 patients in the BiRd group and 18 patients in the Rd group. Of these, 36 deaths (25%) in the BiRd group and 22 deaths (15%) in the Rd group were due to SAEs. The most frequently reported SAEs resulting in death were infections, leading to the death of 14/143 patients (10%) and 7/143 patients (5%) in the BiRd and Rd groups, respectively.

Among the patients in the BiRd cohort, four patients (3%) developed second primary malignancies: solid tumors in four patients and one hematologic cancer. In the Rd cohort, only one patient (1%) developed a solid tumor.

The mean RDI of clarithromycin was 80%. The RDI of lenalidomide was 72.1% in patients in the BiRd group and 83.3% in patients in the Rd group. As for dexamethasome, the RDI was 62.8% in the BiRd group and 84.3% in the Rd group. The percentage of patients who were forced to modify the dose of lenalidomide was 54.5% in the BiRd group and 51% in the Rd group. Regarding dexamethasome, the percentage of patients who had to modify their dose was

49.6% in the BiRd group and 46.5% in the Rd group. One patient in the BiRd regimen was forced to discontinue lenalidomide treatment; 6 patients in the BiRd regimen and 4 patients in the Rd regimen terminated dexamethasome treatment and a total of 16 patients discontinued clarithromycin treatment.

3.9. Conclusions

Retrospective and phase-II studies had previously shown that the administration of clarithromycin in combination with immunomodulatory drugs such as thalidomide, pomalidomide, or lenidomide in patients with relapsed or newly diagnosed MM was superior to treatment with immunomodulatory drugs alone. Hitherto, phase-III study assesing the efficacy and safety of combining clarithromycin with immunomodulatory drugs to treat newly diagnosed MM patient ineligible for autologous transplantation had never been performed. To this aim, we decided to conduct the present phase-III study. Our hypothesis was that the addition of clarithromycin to lenalidomide and dexamethasome (BiRd treatment) would result in a greater PFS than that of patients who were administered lenalidomide and dexamethasome alone (Rd tratment). In contrast to our hypothesis and against the results of previous studies, our results showed that the BiRd regimen did not yield a longer median PFS than that observed in Rd patients (23 months in the BiRd group vs 29 months in the Rd group), despite the CR of the BiRd regimen being higher than that of the Rd regimen (22.6% vs 14.4%, p=0.048). Regarding the safety profile, the most frequently observed grade 3-4 AEs were neutropenia and infections, with similar incidences in both treatment arms: 12% (BiRd) vs 19% (Rd) and 30% vs 25%, respectively.

These results could be partially explained by the age of the cohort in our clinical trial: more than half of the patients included in this study were ≥75 years old. Within this subgroup of patients, the PFS of those who had been treated with BiRd was shorter than that of patients treated with Rd (19 vs 28 months, p=0.05). However, the mean TTP detected in BiRd patients older or 75 years of age was similar to that of those in the Rd group, suggesting the existence of a higher number of deaths due to treatment. In fact, the number of deaths unrelated to disease progression among patients ≥75 years old was higher in the BiRd group (26/50) than in the Rd group (16/40). This trend may be explained by the stabilizing effect of clarithromycin on the half-life of steroids, slowing their clearing from the human body and potentially leading to steroid overexposure.

In conclusion, further studies adjusting clarithromycin and steroids dose according to patient's age and functional status will be required in the future to maximize the benefits of this

treatment in MM patients ineligible for transplantation. Moreover, the results of our study highlight the importance of conducting phase-III studies to confirm the validity of the results obtained in phase I/II studies.

Signature.:

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Dr. Mª Victoria Mateos Manteca

Main study coordinator

Appendix 1: List of participating centres

CENTRE	PRINCIPAL INVESTIGATOR	ENROLLED PATIENTS
Complejo Hospitalario de Navarra	Dr. Jose María Arguiñano Pérez	9
Hospital Costa del Sol (Marbella)	Dra. Ricarda García Sánchez	6
Hospital Universitario Virgen de la Victoria (Málaga)	Dra. Laura Rosiñol Dachs	10
Hospital Universitario Virgen del Rocío (Sevilla)	Dra. Marta Reinoso Segura	8
Hospital Universitario de Santiago de Compostela	Dra. Marta Sonia González Pérez	3
Hospital Universitari Germans Trias i Pujol	Dr. Albert Oriol Rocafiguera	18
Hospital Clínic de Barcelona	Dr. Joan Bladé Creixentí	28
Hospital de Cabueñes (Gijón)	Dra. María Esther González García	27
Hospital de León	Dr. Fernando Escalante Barrigón	17
Hospital G. Universitario Morales Meseguer (Murcia)	Dr. Felipe de Arriba de la Fuente	20
Hospital Universitario Virgen de Valme (Sevilla)	Dra. María del Carmen Couto Caro	8
Hospital Universitario 12 de Octubre (Madrid)	Dr. Joaquin Martínez López	10
Hospital Universitario de Canarias	Dr. Miguel Teodoro Hernández García	31
Hospital Universitario de la Princesa (Madrid)	Dr. Adrián Alegre Amor	9
Hospital Universitario de Salamanca	Dra. María Victoria Mateos Manteca	19
Hospital UniversitarioDr. Peset (Valencia)	Dra. Paz Ribas García	14
Hospital General de Castellón	Dra. Adriana Gascón Buj	0
Hospital Universitario Politécnico La Fe (Valencia)	Dr. Isidro Jarque Ramos	6
Hospital Universitario Virgen de las Nieves (Granada)	Dra. Esther Clavero Sánchez	13
Hospital Universitario Vall d'Hebrón (Barcelona)	Dra. Mercedes Gironella Mesa	14
Hospital Gregorio Marañón	Dra. Cristina Encinas	2
Hospital Clínico Universitario de Valencia	Dra. Anabel Teruel	1
Hospital Txagorritxu	Dr. Buenaventura Buendía Ureña	4
Hospital Universitario Marqués de Valdecilla	Dr. Guillermo Martín Sánchez	3
Hospital del SAS de Jerez	Dr. Sebastián Garzón López	4
CHUAC	Dra. Ana María Vale López	2

Appendix 2: Severe Adverse Events

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
Navarra Hospital Complex	10_341-1	Rd	Pneumonia nosocomial	27.08.2016	10.09.2016	Grade 3/Severe. Prolonged hospitalization	Unrelated	Temporary suspension of medication
	17-341-1	Rd	Bacteraemia and renal failure	27.09.2016	26.10.2016	Grade 3/Severe. Prolonged hospitalization	Unlikely	Temporary suspension of medication
	26,341-2	BiRd	Fever, neutropenia and lymphocitopenia	06.11.2016	17.11.16	Grade1/Hospitalization	Unlikely	Temporary suspension of medication
	42,341-2	BiRd	Diarrhoea	15.01.2017	19.01.17	Grade3/Hospitalization	Likely	Temporary suspension of medication
	46.AAG_341-1	Rd	Pneumonia	27.01.2017	Initial and Final	Grade4 /Death	Likely to dexamethasome and lenalidomide	Medication discontinued due to previous diarrhea
	190.AAG_341-6	BiRd	Moderate acute renal failure + hyperkalaemia + digitalis poisoning and ultrasound cholecystitis	28.01.2018	27.02.18	Grade3/Hospitalization	Likely to dexamethasome and lenalidomide	Temporary suspension of medication
	191.AAG_341-8	BiRd	Death	31.01.2018	Initial and Final	Grade 4 / Death	Likely to lenalidomide, dexamethasome and clarithromycine	Permanently discontinued due to this event
	212.AAG_341-2	BiRd	Fever due to urinary tract infection	03.03.2018	12.03.2018	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	223.AAG_341-6	BiRd	Decompensated congestive heart failure	24.03.2018	08.04.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	241.AAG_341-6	BiRd	Amyloidosis	19.04.2018	Initial and Final	Major medical event	Unrelated	Permanently discontinued due to this event
	324.AAG_341-2	BiRd	Basal cell carcinoma	6.9.2018	6.9.2018	Grade3 / Major medical event	Likely to lenalidomide	Dose continues unchanged

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
			Basal cell carcinoma	26.11.2018	Initial and Final	Grade3 / Major medical event	Likely to lenalidomide	
	407. AAG_341-4	Rd	Febrile syndrome secondary to study treatment	21.03.2019	05.04.2019	Grade2/Hospitalization	Likely to Lenalidmide and Dexamethasome	Patient does not resume taking the study medication (Lenalidomide, Dexamethasome).
	509. AAG_341-4	Rd	Astenia	26.09.2019	Initial and Final	Grade 3 / Major medical event	Likely to study medication	Permanent discontinuation of medication
	533.AAG_341-11	BiRd	Hypocalcaemia	10.12.2019	16.12.2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	574. AAG_341-11	BiRd	Fever	03.08.2020	17.08.2020	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	617. AAG_341-11	BiRd	adenocarcinoma of the liver	26.05.2021	ongoing	Grade 4/ life-threatening	likely to lenalidomide	Permanent discontinuation of treatment by this EC
Costa del Sol Hospital	47.AGG_342-1	Rd	Septic shock	09.12.2016	29.12.2016	Grade4 / life-threatening	Unrelated	Discontinued permanently due to SAE
	80.AAG_342-5	Rd	Nausea, vomiting, bradycardia	24.05.2017	03.07.2017	Grade3/Hospitalization	Likely to lenalidomide and possibly to dexamethasome	Suspensión permanente de Lenalidomide
	102.AAG_342-2	Rd	Deep vein thrombosis	26.07.2017	01.08.2017	Grade3/Hospitalization	Unrelated	NA
	304.AAG_342-6	BiRd	Perforated diverticulitis	13.08.2018	22.08.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	619. AAG_342-6	BiRd	Pelvic pain	25.05.2021	26.06.2021	Grade 2 - moderado/ Hospitalization	Unrelated	Completely resolved
Virgen de la Victoria University Hospital	29_343-1	Rd	Left hip fracture	16.11.2017	13.01.2017	Grade 3/Severe. Hospitalization/Prolonged hospitalization	Unrelated	Temporary suspension of medication
	30_343-1	Rd	Upper gastrointestinal bleeding secondary to gastrointestinal injury	16.11.2017	13.01.2018	Grade3 /Hospitalization	Likely to dexamethasome	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	74, AAG_343-1	Rd	Prolonged hospitalization due to scheduled surgery	22.02.2017	20.03.2017	Grade3 /Hospitalization	Unrelated	Temporary suspension of medication
	143.AAG_343-5	Rd	Urinary tract infection	20.10.2017	25.10.2017	Grade 3/Hospitalization	Possibly to lenalidomide, unlikely to dexamethasome	Temporary suspension of medication
	180.AAG_343-2	Rd	Influenza A	07.01.2018	16.01.2018	Grade 3/Hospitalization	Possibly to Lenalidomide and Dexamethasome	Temporary suspension of medication
	196. AAG_343-2	Rd	Acute ischaemic stroke	30.01.2018	05.02.2018	Grade 3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	269.AAG_343-9	BiRd	Confusional state	29.05.2018	05.06.2018	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	288. AAG_343-10	BiRd	Heart failure	04.07.2018	05.07.2018	Grade4/Life-threatening	Unrelated	Dose continues unchanged
	294. AAG_343-9	BiRd	Pneumonia	09.07.2018	Initial and Final	Grade4/Death	Unrelated	Medication permanently discontinued due to this event
	312. AAG_343-1	Rd	Pneumonia	23.08.2018	07.09.2018	Grade 3/Hospitalization	Unrelated	NA
	399,AAG_343-12	BiRd	Worsening renal function, hypokalaemia, hypokalaemia, hypocalcaemia	06.03.2019	06.03.2019	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	416.AAG_343-12	BiRd	Hypocalcaemia severe	05.04.2019	10.04.2019	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	422.AAG_343-6	BiRd	Acute diverticulitis with perforation	08.04.2019	21.04.2019	Grade4/Life-threatening	Unrelated	Temporary suspension of medication
	456.AAG_343-2	Rd	Pneumonia	16.06.2019	24.06.2019	Grade4/Hospitalization	Unrelated	Dose continues unchanged
	472.AAG_343-14	BiRd	Diabetic coma	21.07.2019	23.07.2019	Grade 4/Hospitalization/Life-threatening	Unrelated	Temporary suspension of medication
	480.AAG_343-8	Rd	Left foot cellulitis and heart failure	06.08.2019	Initial and Final	Grade 4/Death	Unrelated	Permanent discontinuation of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	498.AAG_343-8	Rd	Death due to multi-organ heart failure secondary to cellulitis infection.	19.08.2019	Initial and Final	Grade 4/Death	Unrelated	Permanent discontinuation of medication
	548.AAG_343-2	Rd	Dyspnoea	07.01.2020	30.01.2020	Grade 4/Hospitalizationy life-threatening	Unrelated	Temporary suspension of medication
Virgen de la Victoria University Hospital	550.AAG_343-12	BiRd	Pneumonia and Influenza HIN1	16.01.2020	23.01.2020	Grade 2/Hospitalizationy life-threatening	Unrelated	Dose continues unchanged
	555. AAG_343-14	BiRd	Hip fracture	03.02.2020	13.02.2020	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	556. AAG_343-12	BiRd	Pneumonia	24.02.2020	06.03.2020	Grade 4/Life-threatening	Unrelated	Permanent discontinuation of medication
	650.AAG_343-14	BiRd	Sepsis of pulmonary origin, with bilateral Pneumonia	10.02.2020	Ongoing	Grade 3/Hospitalization	Unrelated	Permanent discontinuation of medication
Virgen del Rocío University Hospital	13-344-1	BiRd	urinary tract infection	15.09.2016	26.09.2016	Grade 2/Moderate Hospitalization/Prolonged hospitalization	Likely to lenalidomide, dexamethasome and clarithromycine	Temporary suspension of medication
	79.AAG_344-5	BiRd	Sepsis	21.06.2017	27.06.2017	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	84.AAG_344-3	Rd	Acute calculous cholecystitis	01.07.2017	Initial and Final	Grade3/Hospitalization	Unrelated	NA
	96-344-2	BiRd	Renal Impairment	26.07.2017	22.08.2017	Grade 3/Severe. Hospitalization/Prolonged hospitalization	Possibly to Clarithromycine	Temporary suspension of medication
	254.AAG_344-5	BiRd	Acute renal failure	01.05.2018	08.05.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
			Renal failure	08.05.2018	End of patient participation in the study	Grade 4/ Hospitalization/Persistent or significant disability or incapacity/Major medical event	Unrelated	Permanent discontinuation of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	495.AAG_344-6	BiRd	Toxicity due to clarithromycin	09.07.2018	27.07.2018	Grade 3/Persistent or significant disability or incapacity	Possible to Dexamethasome and Clarithromycine	Lenalidomide unchanged, reduced Dexamethasome and Clarithromycine permanently suspended
	656.AAG_344-8	Rd	Pneumonia	15.03.2023	11.04.2023	Grade 2 / Moderate Hospitalization	Unrelated	Hospitalization Antibiotic treatment Dexamethasome and Lenalidomide unchanged
	543.AAG_344-1	BiRd	Viral Hepatitis Reactivation (HBV)	30.12.2019	ongoing	Grade 3/severe	Unrelated	Dose continues unchanged
Santiago de Compostela University Hospital	33_345-1	BiRd	Pneumonia	21.11.2016	02.12.2016	Grade 3/ Hospitalization	Unrelated	Resolved
	49, AAG_345-2	Rd	Pneumonia	13.02.2017	13.02.2017	Grade 3/ Hospitalization	Likely to lenalidomide and to dexamethasome.	Temporary suspension of medication
	54. AAG_345-2	Rd	Acute renal failure	13.02.2017	Initial and Final	Grade 3/ Hospitalization	Likely to Lena and unlikely to Dexa	Permanent discontinuation of medication
Germans Trias i Pujol University Hospital	116_346-2	Rd	Febrile neutropenia	08.09.17	13.09.17	Grade 2 / Moderate Hospitalization	Likely to lenalidomide and to Dexamethasome	Temporary suspension of medication
	157.AAG_346.3	BiRd	Acute pulmonary oedema	04.12.2017	20.12.20107	Grade 2 / Moderate Hospitalization	Unrelated	NA
	182. AAG_346.3	BiRd	Respiratory failure	08.01.2018	22.01.2018	Grade 2 / Moderate Hospitalization	Unrelated	Dose continues unchanged
	192.AAG_346-3	BiRd	Skin rash	20.01.2018	10.02.2018	Grade 3/Major medical event	Likely to lenalidomide	Temporary suspension of medication
	195. AAG_346.3	BiRd	Syncope	01.02.18	16.02.2018	Grade 2 / Moderate Hospitalization	Unrelated	Temporary suspension of medication
	213.AAG_346.7	BiRd	Respiratory infection	05.03.2018	13.03.2018	Grade 2 / Moderate Hospitalization	Unrelated	Temporary suspension of medication
	217.AAG_346.4	Rd	Respiratory infection	09.03.2018	Initial and Final	Grade 4/Death	Unrelated	Dose continues unchanged
	239.AAG_346.10	BiRd	Respiratory infection	16.02.2018	24.04.2018	Grade 2/Hospitalization	Unrelated	Temporary suspension of medication
	272.AAG_346-3	BiRd	Febrile neutropenia	03.06.2018	05.06.2018	Grade 2/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
Germans Trias i Pujol	274.AAG_346-7	BiRd	Septic shock	05.06.2018	21.06.2018	Grade 4/Hospitalization	Likely to lenalidomide and posibbly to	Definitive suspension of Lenalidomide and temporary suspension of Dexamethasome and Clarithromycine.

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
University Hospital							dexamethasome and clarithromycine	
	285.AAG_346-8	Rd	Pulmonary embolism	24.06.2018	02.07.2018	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspendion of Lenalidomide and Dexamethasome
	287.AAG_346-13	BiRd	Diarrhea	04.07.2018	11.07.2018	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	332.AAG_346-19	Rd	Septic shock	24.10.2018	Initial and Final	Grade4/Death	Unrelated	NA
	347.AAG_346-5	Rd	Fever	10.12.17	06.01.2018	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	351.AAG_346-18	Rd	Intestinal ischaemia	10.12.17	ongoing	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	382.AAG_346-18	Rd	Respiratory infection due to influenza A virus	06.02.2019	15.02.2019	Grade2/Moderate	Unrelated	Temporary suspension of medication
	434.AAG_346-5	Rd	Adenocarcinoma of colon	18.04.2019	ongoing	Grade 3/Major medical event	Likely to lenalidomide and unlikely to dexamethasome and clarithromycine	NA
	496.AAG_346-15	BiRd	Respiratory infection por Streptococcus Pneumoniae	20.08.19	13.09.19	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	499.AAG_346-20	BiRd	Heart failure	14.08.2019	29.08.2019	Grade 3/Hospitalization	Unrelated	Temporary suspension of Clarithromycine
	565. AAG_346-17	Rd	Spinal cord compression	29.03.2020	ongoing	Grade 3/Hospitalization	Unrelated	Permanent discontinuation as of 03/06/2020
	591. AAG_346-14	BiRd	Adenocarcinoma of colon	07.06.2019	ongoing	Grade 3/Major medical event	Likely to lenalidomide, dexamethasome and clarithromycine	Medication permanently suspended due to this adverse event.
Barcelona Clinic Hospital	652.AAG_347-30	Rd	E.coli sepsis of urinary origin	16.04.2023	ongoing	Grade 3/Severe Hospitalization	Unrelated	Hospitalization Antibiotic treatment Retained GEM-CLARIDEX medication
	653.AAG_347-05	BiRd	S. Aureus sepsis	03.05.2023	09.06.2023	Grade 3/ Severe Hopitalización	Unrelated	Hospitalization Antibiotic treatment Retained GEM-CLARIDEX medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	654.AAG_347-29	Rd	Pancreatic mass	16.05.2023	02.06.2023	Grade 3/ Severe Hopitalización	Possibly related	Hospitalization Temporary suspension of clinical trial treatment.
Cabueñes Hospital	233.AAG_348-2	BiRd	Ischaemic infarction	19.05.2018	25.05.2017	Grade 2/Hospitalization	Likely to lenalidomide and dexamethasome	Temporary suspension of medication
	207.AAG_348-26	BiRd	Respiratory infection and shoulder contusion	15.01.2018	06.02.2018	Grade 3/Hospitalization	Likely to lenalidomide	Permanent discontinuation due to this event
	482.AAG_348-4	Rd	Pneumonia left upper lobe	11.05.2017	03.06.2017	Grade 3/Hospitalization	Unrelated	Permanent discontinuation due to this adverse event
	483.AAG_348-14	Rd	Dyspnoea and Fever	16.10.2017	16.10.2017	Grade 3/Hospitalization	Unrelated	Permanent discontinuation due to this adverse event
	484.AAG_348-12	BiRd	Heart failure with Respiratory infection	09.01.2018	09.01.2018	Grade 3/Hospitalization	Unrelated	Permanent discontinuation due to this adverse event
	485.AAG_348-18	Rd	Toxicity to treatment	02.11.2017	02.11.2017	Grade 3/Hospitalization	Definitive	Permanent discontinuation due to this adverse event
	487.AAG_348-22	BiRd	Neurotoxicity	14.02.2018	04.04.2018	Grade3.Disability and major medical event	Definitive to Lenalidomide and likely to Dexamethasome and Clarithromycine	Permanent discontinuation due to this adverse event
	524.AAG_348-28	BiRd	Pneumonia	24.10.2019	20.11.2019	Grade 2/Hospitalization	Unrelated	Temporary suspension of medication
	642_AAG_348-9	Rd	Fracture by fall	06.09.2022	ongoing	Grade 3 /Severe – hospitalization and relevant medical significance	Unrelated. Remains unchanged	Unrelated. Remains unchanged
León Hospital	77.AAG_349-1	BiRd	Respiratory infection	13.05.2017	23.05.2017	Grade /Hospitalization	Unrelated	None
	144.AAG_354-4	BiRd	Confusional Syndrome	27.10.17	31.10.17	Grade 2 /Hospitalization	Unrelated	Temporary suspension of medication
	145.AAG_349-14	BiRd	Septic shock	27.10.2017	Initial and Final	Grade 5/Death	Likely to lenalidomide and dexamethasome	Permanent discontinuation due to this adverse event
León Hospital	149.AAG_349-16	BiRd	Hyperglycaemia	19.11.17	27.11.17	Grade 2 /Hospitalization	Likely a dexamethasome and unlikely to clarithromycine	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	169.AAG_349-16	BiRd	Respiratory failure	26.12.17	29.01.18	Grade 3/Hospitalization and major medical event	UnLikely to lenalidomide, Dexamethasome and Clarithromycine	Permanently discontinued due to this event. The patient no longer receives study medication.
	193.AAG_349-4	Rd	Pneumonia	30.01.2018	22.03.2018	Grade 3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	209.AAG_349-3	Rd	Dislocation of the left hip prosthesis	15.02.2018	23.02.2018	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	228.AAG_349-3	Rd	Dislocation of the left hip prosthesis	25.02.2018	28.02.2018	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	244.AAG_349-21	BiRd	Sepsis of urinary origin	20.04.2018	28.04.2018	Grade 3/Hospitalization	Likely to lenalidomide, dexamethasome and clarithromycine	Temporary suspension of medication
	275.AAG_349-17	BiRd	Acute pancreatitis	04.06.2018	04.06.2018	Grade 3/Life-threatening + Hospitalization+ Major medical event	Unlikely (Clarithromycine)	Temporary suspension of medication
	276.AAG_349-23	Rd	Respiratory infection	07.06.2018	19.06.2018	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	370.AAG_349-23	Rd	Analytical tests compatible with congestive heart failure.	20.01.2019	20.01.2019	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	451.AAG_349-3	Rd	Complete atrioventricular block	29.05.2019	04.06.2019	Grade 3/Hospitalization-Major medical event	Unrelated	Permanent discontinuation due to this adverse event
	500.AAG_349-28	Rd	Psychomotor agitation	05.08.2019	07.08.2019	Grade 3/ Major medical event	Likely to study medication	Temporary suspension of Lenalidomide and reduction of Dexamethasome
	526. AAG_349-27	Rd	Haematuria	21.11.2019	09.01.2020	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
León Hospital	557.AAG_349-3	Rd	Fourth episode of left hip dislocation	11.02.2020	27.02.2020	Grade 3/Hospitalization	Unrelated	Unchanged
	559. AAG_349-8	Rd	COVID19 Positive	01.04.2020	10.04.2020	Grade 3	Unrelated	Temporary suspension of medication
	560. AAG_349-25	Rd	COVID19 Positive	17.04.2020	17.04.2020	Grade 3	Unrelated	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	562. AAG_349-25	Rd	Hip fracture	08.05.2020	08.05.2020	Grade 3/Hospitalization	Unrelated	The patient no longer receives study medication.
	564. AAG_349-1	BiRd	Cholecystitis with gallstones	09.05.2020	28.05.2020	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	585.AAG_349-28	Rd	Dysatria	02.10.2020	04.10.2020	Grade 3/Hospitalization	Unrelated	Unchanged
	629.AAG_349-3	BiRd	Death without apparent cause	15.12.2021	15.12.2021	Death	Unrelated	The cause is yet to be determined.
Morales Meseguer University Hospital	05_351-1	BiRd	Deterioration of general condition	02.08.2016	Completely resolved 05.08.16	Grade 3/Severe. Hospitalization/Prolonged hospitalization	Unrelated	Temporary suspension of medication
	55.AAG_351-4	Rd	Urinary tract infection	26.02.2017	09.03.2017	Grade 3	Unrelated	Temporary suspension of medication
	60.AAG_351-3	BiRd	Acute renal failure	31.03.2017	10.04.2017	Grade 3 /Hospitalization	Discontinued permanently due to SAE	Completely resolved
	83.AAG_351-2	BiRd	Non-neutropenic fever. Pneumonia with middle lobe focus.	03.07.2017	03.07.2017	Grade 3/Hospitalization	Unrelated	Temporary suspension of Clarithromycine
	111.AAG_351-5	BiRd	Traumatic brain injury	04.09.2017	13.09.17	Grade 3/Hospitalization	Unrelated	Temporary suspension of Clarithromycine
	150.AAG_351-5	BiRd	Acute Respiratory Failure	26.11.2017	19.12.2017	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	170.AAG_351-6	Rd	Hypotension	28.12.2017	ongoing	Grade 2/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
Morales Meseguer University Hospital	211.AAG_351-15	BiRd	Dysphagia	01.03.2018	16.03.2018	Grade 3/Hospitalization	Possibly to dexamethasome	Temporary suspension of medication
	220.AAG_351-14	BiRd	ST-segment elevation acute coronary syndrome: minor myocardial infarction	10.03.2018	15.03.2018	Grade 3/Hospitalization	Unrelated	Unchanged
	227.AAG_351-15	BiRd	Pneumonia	31.03.2018	19.04.2018	Grade 3/Hospitalization	Unrelated	NA
	236.AAG_351-14	BiRd	Pneumonia	12.04.2018	24.04.2018	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	237.AAG_351-14	BiRd	Vertebral compression fractures	12.04.2018	24.04.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	255.AAG_351-16	BiRd	Impaired renal function	02.05.2018	09.05.2018	Grade3/Hospitalization	Likely to lenalidomide, unlikely to dexamethasome and clarithromycine	Temporary suspension of medication
	258.AAG_351-16	BiRd	Impaired renal function	15.05.2018	18.05.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	262.AAG_351-6	Rd	Febrile neutropenia, Likely urinary focus	19.05.2018	25.05.2018	Grade3/Hospitalization	Likely to lenalidomide and dexamethasome	Temporary suspension of medication
	263.AAG_351-16	BiRd	Diarrhea	22.05.2018	ongoing	Grade3/Hospitalization	Likely to lenalidomide. Unrelated to dexamethasome or clarithromycine	Temporary suspension of medication
	279.AAG_351-17	BiRd	Neutropenic fever. Likely urinary focus	16.06.2018	16.06.2018	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	298.AAG_351-6	Rd	Fever without focus	30.07.2018	10.08.2018	Hospitalization	Unrelated	Dose continues unchanged
	299.AAG_351-13	Rd	Diarrhea	07.08.2018	13.08.2018	Hospitalization	Unrelated	Temporary suspension of medication
	01.AAG_351-6	Rd	Fever nosocomial without focus	13.08.2018	17.08.2018	Grade3 / Hospitalization	Unrelated	Dose continues unchanged
Morales Meseguer University Hospital	311.AAG_351-18	Rd	Sepsis of respiratory origin. Pneumonia	24.08.2018	31.08.2018	Grade3 / Hospitalization	Likely to lenalidomide and Dexamethasome	Temporary suspension of medication
	321.AAG_351-21	BiRd	Fever	03.10.2018	17.10.2018	Grade3 / Hospitalization	Unrelated	Temporary suspension of medication
	330.AAG_351-22	Rd	Right-sided Pneumonia and middle and lower lobes of the lungs	29.10.2018	09.11.2018	Grade3/Hospitalization	Unlikely to study medication	Temporary suspension of medication
	336.AAG_351-10	Rd	Haemodynamic angina pectoris secondary to atrial fibrillation	17.11.2018	20.11.2018	Grade3/Hospitalization	Unlikely to study medication	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
			with rapid ventricular response					
	337.AAG_351-21	BiRd	Generalised rash and worsening general condition	20.11.2018	07.12.2018	Grade3/Hospitalization	Likely to Lena and Clari.	Permanently discontinued due to this event
	339.AAG_351-1	Rd	Ataque isquémico transitorio	20.11.2018	23.11.2018	Grade3/Hospitalization	Likely to lenalidomide.	NA
	349.AAG_351-10	Rd	Pneumonia LII	08.12.2018	14.12.2018	Grade3/Hospitalization	Unrelated	NA
	350.AAG_351-5	BiRd	Probably pharmacological acute renal failure	10.12.2018	22.12.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	357.AAG_351-13	Rd	Proctalgia	18.12.2018	19.12.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	373.AAG_351-5	BiRd	Exacerbation of mixed-cause chronic renal failure	25.01.2019	29.01.2019	Grade3/Hospitalization	Possibly to Lenalidomide and unlikely to Clarithromycine	Temporary suspension of medication
	379.AAG_351-16	BiRd	Unstable angina	22.05.2018	01.06.2018	Hospitalization	Unrelated	Temporary suspension of medication
	381.AAG_351-5	BiRd	Respiratory infection	27.01.2019	06.02.2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
Morales Meseguer University Hospital	386.AAG_351-1	BiRd	Influenza A	15.02.2019	15.02.2019	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	415.AAG_351-19	BiRd	Respiratory septic shock	03.04.2019	4.04.2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	432.AAG_351-7	Rd	Pneumonia	30.04.2019	06.05.2019	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	506.AAG_351-6	Rd	Febrile neutropenia	10.09.2019	10.09.2019	Grade 3/Hospitalization	Possibly	Temporary suspension of medication
	517. AAG_351-2	BiRd	Complicated wound with exposed tendon in the left foot	08.09.2019	08.09.2019	Grade 3/Hospitalization	Unrelated	Permanent discontinuation of medication
	527. AAG_351-4	Rd	Acute Bronchitis	02.12.2019	12.12.2019	Grade 3/Hospitalization	Unrelated	Permanent discontinuation of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	569. AAG_351-9	Rd	Confusing multifactorial síndrome. Likelymente debido a urinary tract infection	04.07.2020	14.07.2020	Grade 4 - life-threatening /Hospitalization	Unrelated	Permanent discontinuation of medication
	576.AAG_351-4	Rd	SARS-COV-2 Positive	08.09.2020	17.09.2020	Grade 2/Major medical event	Unrelated	Permanent discontinuation of medication
	581. AAG_351-6	Rd	Pneumonia of the left lower lobe	09.10.2020	19.10.2020	Grade 3/Hospitalization	Unrelated	Permanent discontinuation of medication
	620. AAG_351-4	Rd	Cranial nerve VI paralysis	14.07.2021	22.07.2021	Grade 3 - Severe/ Hospitalization	Unrelated	Permanentsuspension of medication due to this adverse event
Virgen de Valme University Hospital	85.AAG_352-4	BiRd	Hyperosmolar syndrome	04.07.2017	Initial and Final	Grade 4/Life-threatening Hospitalization/Prolonged hospitalization/Death	Definitive to Lenalidomide and likely to Dexamethasome	Temporary suspension of Lenalidomide and Dexamethasome
	126.AAG_352-2	Rd	Acute kidney injury	27.09.2017	08.10.2017	Grade3/Hospitalization	Unrelated	NA
	140.AAG_352-2	Rd	Suspected invasive fungal infection	04.10.2017	15.10.2017	Grade4/Death	Unrelated	NA
Virgen de Valme University Hospital	152.AAG_352-6	Rd	Respiratory infection	29-11-2017	12-12-20107	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	153.AAG_352	Rd	Vomiting	26-11-2017	15-12-20107	Grade 4/life threatening	Likely to lenalidomide	Temporary suspension of medication
	162.AAG_352-6	Rd	Flu	18-12-2017	24-12-2017	Grade 2/Hospitalization	Unrelated	Temporary suspension of medication
	172.AAG_352-5	Rd	Flu	24-12-2017	29-12-2017	Grade 4/Hospitalization +Death	Unrelated	Dose continues unchanged
	174.AAG_352-6	Rd	Bacteremia due to S. hominis	01-01-2018	08-01-2018	Grade 2/Hospitalization	Unrelated	Dose continues unchanged
	177.AAG_352-6	Rd	Bacteremia due to S. hominis	28-11-2017	28-11-2017	Grade 2/Significant Medical Condition	Unrelated	Dose continues unchanged
	322.AAG_352-10	BiRd	Presyncope	8-10-2018	15-10-2018	Grade2 / Hospitalization	Unrelated	Temporary suspension of medication
	518. AAG_352-10	BiRd	Death	11.09.2019	Initial and Final	Grade 4/ Death	Unrelated	NA

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
12 de Octubre University Hospital	07_353-3	Rd	Pulmonary thromboembolism	07-08-16	05-09-16 resolved with sequels	Grade 3/Severe. Hospitalization/Prolonged hospitalization	Likely to lenalidomide and unlikely to dexamethasome	Temporary suspension of medication
	99_353-7	BiRd	Glycemic decompensation	25-07-17	27-07-17	Grade 4/Life-threatening. Hospitalization/Prolonged hospitalization	Likely	Temporary suspension of dexamethasome
	108.AAG_353-8	Rd	Cardiogenic shock and rash	29-08-17	08-09-17	Grade 3/Hospitalization	Likely to lenalidomide	Continues unchanged
	110.AAG_353-7	Rd	Acute pulmonary oedema	01-09-17	08-09-17	Grade3/Hospitalizationy life-threatening	Unrelated	Temporary suspension of medication
	135_353-8	Rd	Decompensated heart failure	13.10.2017	13.10.2017	Grade2/Hospitalization	Unrelated	Continues unchanged
	142,AAG_353-8	Rd	Constipation	24.10.2017	24.10.2017	Grade 2/Hospitalization	Likely to lenalidomide	Continues unchanged
	156.AAG_353-8	Rd	Constipation	04.12.2017	04.12.2017	Grade 2/Hospitalization	Definitive to Lenalidomide	Continues unchanged
12 de Octubre University Hospital	283.AAG_353-10	BiRd	Epistaxis	15-06-2018	17-06-2018	Grade1/Hospitalization	Unrelated	Temporary suspension of Clarithromycine
	345.AAG_353-9	Rd	Progressive disease	29-11-2018	09-12-2018	Grade4/Hospitalization	Unrelated	Permanently discontinued due to this event
	433.AAG_353-19	BiRd	Decompensated heart failure	02/05/2019	10/05/2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	452.AAG_353-14	Rd	Severe symptomatic aortic stenosis	05/06/2019	11/06/2019	Grade3/Hospitalization	Unrelated	Permanently discontinued because of this EC
	515.AAG_353-19	BiRd	Degenerative aortic insufficiency	05/06/2019	11/06/2019	Grade3/Hospitalization	Unrelated	Permanently discontinued because of this EC
	540.AAG_353-19	BiRd	Left costal pleuritic pain	06/12/2019	13/12/2019	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	545.AAG_353-19	BiRd	Respiratory infection	08.01.2020	08.01.2020	Grade 2/ Hospitalization	Unrelated	Temporary suspension of medication
	572. AAG_353-10	BiRd	Squamous cell skin cancer	27/06/2019	27/06/2019	Grade3/Hospitalization	Likely to lenalidomide	NA

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
Canary University Hospital	645_AAG_ 354-10	BiRd	Respiratory infection	03.11.2022	03.11.2022	Grade 3/ Severe Hospitalization	Possibly related to lenalidomide	Withheld GEM-CLARIDEX medication
University Princess's Hospital	25.355-1	BiRd	Respiratory infection	27-10-2016	24/11/2016	Grade 2/ Hospitalization	Unrelated	Temporary suspension of medication
	65.AAG_35 5-6	Rd	COPD	24/04/2017	26/04/2017	Grade2/Hospitalization	Unrelated	None
	94.355-5	BiRd	Hepatotoxicity	11/07/2017	01/09/2017	Grade 3/ Major medical event	Unrelated	Temporary suspension of medication
	122.AAG_3 55-4	Rd	Rectal bleeding	10-09-2017	14-09-2017	Grade2/Hospitalization	Likely to lenalidomide	Temporary suspension of lenalidomide.
	181.355-6	Rd	Pneumonia	14-12-2017	19-12-2017	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	203. AAG_355-7	Rd	Respiratory infection	17/02/2018	08/03/2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
University Princess's Hospital	610. AAG_355-7	Rd	Cardiac failure	16/02/2021	08/03/2018	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	315.AAG_3 55-1	BiRd	Femur fracture	30/08/2018	05/09/2018	Grade 3/Hospitalization	Unrelated	Suspension
	354.AAG_3 55-6	Rd	COPD	30/08/2018	05/09/2018	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	355.AAG_3 55-6	Rd	Hip fracture	09.04.2021	09.04.2021	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	403.AAG_3 55-11	Rd	Right pleural effusion	12.03.2019	12.03.2019	Grade3/Hospitalization	Unlikely	Temporary suspension of medication
	622. AAG_355-6	Rd	Inguinal hernia	19.08.2021	19.08.2021	Grade 2 - Moderate/ Hospitalization	Unrelated	Dose continues unchanged
				26.10.2021	26.10.2021	Grade 2 - Moderate/ Hospitalization	Unrelated	Permanent discontinuation of medication
	627. AAG_355-9	BiRd	Colon neoplasia	26.10.2021	26.10.2021	Grade 3 - severe/ Acontecimiento médico relevante	Unrelated	Permanently discontinued because of this EC
Salamanca University Hospital	19-356-2	Rd	Sepsis	29-09-2016	29-09-2016	Grade 3/Severe. Hospitalization/Prolonge d hospitalization	Unrelated	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	64.AAG_356-6	BiRd	Pulmonary thromboembolism	21.04.2017	21.04.2017	Grade 3/Hospitalization	Possibly to dexamethasome and lenalidomide abd clarithromycine	Temporary suspension of Dexamethasome. Lenalidomide and Clarithromycine continue unchanged
	66.AAG_356_2	Rd	Sepsis of respiratory and urinary focus	25.04.2017	25.04.2017	Grade 4/Life-threatening Hospitalization/Prolonged hospitalization	Possibly to dexamethasome. UnrelatedLenalidmida	Permanent discontinuation of lenalidomidedexamethasome by AE
	98.AAG_356-6	BiRd	Deteriorating general condition	28.07.2017	28.07.2017	Grade2 /Hospitalization	Unrelated	Temporary suspension of medication
	105.AAG_356-06	BiRd	Deteriorating general condition	25.08.2017	25.08.2017	Grade2 /Hospitalization	Unrelated	Temporary suspension of medication
	107.AAG_356-10	Rd	Septic shock o foco abdominal	28.08.2017	28.08.2017	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	138.AAG_356-03	Rd	Gastrointestinal bleeding	13.10.2017	13.10.2017	Grade2 /Hospitalization	Unlikely to Dexamethasome	Temporary suspension of medication
Salamanca University Hospital	201. AAG_356-15	Rd	Acute renal failure	12.02.2018	12.02.2018	Grade 3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	219.AAG_356-3	Rd	Febrile neutropenia	20.03.2018	20.03.2018	Grade2 /Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	235.AAG_356-14	BiRd	Sepsis	13.04.2018	13.04.2018	Grade 3/Hospitalization	Unrelated	Temporary suspension of medication
	260.AAG_356-15	Rd	Cerebral Ictus	21.05.2018	21.05.2018	Grade 3/Hospitalization	Likely to lenalidomide. Unrelated to dexamethasome	Temporary suspension of medication
	265.AAG_356-14	BiRd	Epilectic state	28.05.2018	28.05.2018	Grade2 /Hospitalization	Unrelated	Temporary suspension of medication
	291. AAG_356-14	BiRd	Abdominal pain	10.07.2018	10.07.2018	Grade2 /Hospitalization	Unrelated	Temporary suspension of medication
	303.AAG_356-11	Rd	Sepsis	17.08.2018	17.08.2018	Grade 3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	561. AAG_356-19	Rd	Febrile syndrome without focus	04.05.2020	04.05.2020	Grade 3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	649. AAG_356-11	Rd	Respiratory infection (upper respiratory tract)	08.02.2023	08.02.2023	Grade 3/ Severe Hospitalization	Possibly related to lenalidomide and dexamethasome	Hospitaliazción Antibiotic treatment. GEM-CLARIDEX medication withheld..

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
Dr. Peset University Hospital	02_357-1	BiRd	Gastrointeritis	27.06.2016	Death	Grade 4/Life-threatening /Prolonged hospitalization	Likely to lenalidomide and likely to clarithromycine	Temporary suspension of medication
	61.AAG_357-6	Rd	Respiratory infeccion	05.04.2017	05.04.2017	Grade 3/Hospitalization	Unrelated	Dose continues unchanged
	62.AAG_357-3	BiRd	General discomfort	19.04.2017	19.04.2017	Grade2 /Hospitalization	Unrelated	Temporary suspension of clarithromycine
	82.AAG_357-03	BiRd	Febrile syndrome with Likely respiratory focus	03.07.2017	03.07.2017	Grade1 /Hospitalization	Unrelated	Temporary suspension of medication
	87.AAG_357-5	BiRd	Respiratory infection	10.07.2017	10.07.2017	Grade1 /Hospitalization	Unrelated	Dose continues unchanged
	100.AAG_357-6	Rd	NSTEACS Acute Coronary Syndrome Without ST Elevation	07.08.2017	07.08.2017	Grade 3/Hospitalization	Likely to lenalidomide and dexamethasome .	Temporary suspension of medication
Dr. Peset University Hospital	103.AAG_357-3	BiRd	Confusional syndrome	16.08.2017	16.08.2017	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	127.AAG_357-5	BiRd	Hepatic lesions	29.09.2017	29.09.2017	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	171.AAG_357-9	Rd	dehiscent surgical wound	02.01.2018	02.01.2018	Grade2/Hospitalization	Unrelated	Dose continues unchanged
	197. AAG_357-2	BiRd	Death due to cardiorespiratory arrest	06.02.2018	Death	Grade 4 / Death	Unlikely	NA
	214.AAG_357-9	Rd	Acute renal failure	08.03.2018	08.03.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	226.AAG_357-11	Rd	Pneumonia	05.04.2018	05.04.2018	Grade2/Hospitalization	Unrelated	Dose continues unchanged
	243.AAG_357-9	Rd	Brain abscess	20.04.2018	20.04.2018	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	361.AAG_357-14	Rd	Acute myocardial infarction	02.01.2019	Death	Grade 4 / Death	Likely to lenalidomide	Permanent suspension
	376.AAG_357-15	Rd	Febrile neutropenia	04.02.2019	04.02.2019	Grade4/Hospitalization	Unrelated	Dose continues unchanged
	383.AAG_357-13	Rd	Pneumonia	11.02.2019	11.02.2019	Grade3/Hospitalization	Unrelated	Dose continues unchanged

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	431.AAG_357-6	Rd	Ictus	30.04.2019	30.04.2019	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspension of lenalidomide
	449. AAG_357-5	BiRd	Hepatic metastasis of first colon neoplasia	03.06.2019	Death	Grade 4 / Death	Unrelated	Permanently discontinued because of this EC
	469.AAG_357-16	BiRd	Acute gastroenteritis	17.07.2019	17.07.2019	Grade2/Hospitalization	Unrelated	Temporary suspension of medication
	508.AAG_357-16	BiRd	Atypical pneumonia	25.09.2019	25.09.2019	Grade2/Hospitalization	Likely to lenalidomide	Temporary suspension of lenalidomide
	537.AAG_357-6	Rd	Acute leukemia	20.12.2019	20.12.2019	Grade3/Hospitalization	Likely to lenalidomide	The patient is out of the study
Dr. Peset University Hospital	554. AAG_357-15	Rd	Febrile neutropenia	07.02.2020	07.02.2020	Grade2/Hospitalization	Unrelated	Dose continues unchanged
	599.AAG_357-10	BiRd	Pneumonia-COVID19	11.02.2021	11.02.2021	Grade2/Hospitalization	Unrelated	Dose continues unchanged
Politécnico La Fe University Hospital	81.AAG_358-0	BiRd	Risk of unstable glucose levels	27.06.2017	27.06.2017	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	234.AAG_358-4	BiRd	Poor clinical condition	13.04.2018	13.04.2018	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	270.AAG_358-05	BiRd	Disabling pain	04.06.2018	04.06.2018	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	364.AAG_358-6	Rd	Respiratory infection of the lower respiratory tract	07.01.2019	07.01.2019	Grade3/Hospitalization	Likely to lenalidomide	Dose continues unchanged
	454.AAG_358-7	BiRd	Acute renal failure	13.06.2019	13.06.2019	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	505.AAG_358-7	BiRd	Acute Bronchitis	04.09.2019	04.09.2019	Grade3/Hospitalization	Likely to lenalidomide	Permanent suspension of lenalidomide
	519.AAG_358-7	BiRd	Acute diverticulitis	25.10.2019	25.10.2019	Grade 4/Life-threatening	Unrelated	Temporary suspension of medication
	534.AAG_358-7	BiRd	Pulmonary infection	11.12.2019	11.12.2019	Grade3/Hospitalization	Unrelated	Suspensión temporal de la medicación
Virgen de las Nieves Hospital	01_359-2	BiRd	Acute pancreatitis	05.06.2016	05.06.2016	Grade3/Severe	Possibly to dexamethasome	Temporary suspension of medication
	48, AAG_359-5	BiRd	Respiratory infeccion, left	09.02.2017	09.02.2017	Grade3/Hospitalization	Likely to lenalidomide	Permanent suspension of lenalidomide

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
			lower limb celulitis					
	123.AAG_359-7	BiRd	Renal and cardiac failure - Sepsis	25.09.2017	25.09.2017	Grade3/Severe	Possibly to dexamethasome and lenalidomide	Temporary suspension of medication
	175.AAG_359-7	BiRd	Influenza A Virus Infection secondary to thrombocytopenia	04.01.2018	04.01.2018	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Dose continues unchanged
	183. AAG_359-1	BiRd	Pneumonia	16.01.2018	16.01.2018	Grade3/Severe	Possibly to dexamethasome and lenalidomide	Temporary suspension of medication
Virgen de las Nieves Hospital	205.AAG_359-7	BiRd	Symptomatic brain tumor	22.02.2018	22.02.2018	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Temporary suspension of medication
	257.AAG_359-9	BiRd	Secondary renal failure (with hypercalcemia)	10.05.2018	10.05.2018	Grade3/Hospitalization	Possibly to dexamethasome , clarithromycine and lenalidomide	Temporary suspension of medication
	316.AAG_359-9	BiRd	Right hip fracture	10.09.2018	10.09.2018	Grade4/Hospitalization	Possibly to dexamethasome	Temporary suspension of medication
	325.AAG_359-11	Rd	Pneumonia	22.10.2018	22.10.2018	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Temporary suspension of medication
	362.AAG_359-1	BiRd	Perianal abscess	03.01.2019	03.01.2019	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Dose continues unchanged
	395.AAG_359-9	BiRd	Sepsis	04.03.2019	04.03.2019	Grade3/Hospitalization	Likely to lenalidomide	Permanent suspension of lenalidomide and clarithromycine
	414.AAG_359-4	Rd	Hernia surgery	08.04.2019	08.04.2019	NA	Unrelated	Temporary suspension of medication
	470.AAG_359-13	Rd	Sepsis of Likely urinary origin	22.07.2019	22.07.2019	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Temporary suspension of medication
	532.AAG_359-12	Rd	Torsade de pointes type ventricular tachycardia	11.12.2019	11.12.2019	Grade3/Hospitalization	UnLikely to lenalidomide	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	573. AAG_359-4	Rd	Second neoplasm (Adenocarcinoma of the colon)	28.07.2020	28.07.2020	Grade 4/Major medical event	Possibly to dexamethasome and lenalidomide	Permanently discontinued due to this AE
	584.AAG_359-13	Rd	Perianal abscess	03.11.2020	03.11.2020	Grade3/Hospitalization	Possibly to dexamethasome and lenalidomide	Completely resolved
	600,AAG_359-8	Rd	Language impairment	11.02.2021	11.02.2021	Grade 4 - Life-threatening /Hospitalization	Possibly to dexamethasome and lenalidomide	Medication continues unchanged
	624. AAG_359-8	Rd	Sepsis of Likely urinary origin	14.09.2021	14.09.2021	Grade 4 - Life-threatening /Hospitalization	Possibly to dexamethasome and lenalidomide	Completely resolved
Vall d'Hebrón University Hospital	623. AAG_360-12	BiRd	reactivation of Herpes Zoster	25.08.2021	25.08.2021	Grade 3 / Severe	Unrelated	Dose continues unchanged
Vall d'Hebrón University Hospital	641_AAG_360-12		Diarrhoea G4	30.08.2022	30.08.2022	Grade 4/Life-threatening - Hospitalization	Unrelated	Dose continues unchanged
Gregorio Marañón Hospital	549.AAG_731-2	BiRd	Subocclusive intestinal obstruction	20.01.2020	20.01.2020	Grade3/Hospitalization	UnLikely to lenalidomide and clarithromycine	Temporary suspension of medication
Valencia Clinic University Hospital	430.AAG_732-1	Rd	Diarrhoea	30.04.2019	30.04.2019	Grade3/Hospitalization	UnLikely to lenalidomide	Temporary suspension of medication
	606. AAG_732-1	Rd	Septic dental focus	22.03.2021	22.03.2021	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	616. AAG_732-1	Rd	Systemic histoplasmosis	23.04.2021	23.04.2021	Grade3/Hospitalization		Temporary suspension of medication
Txagorritxu Hospital	367.AAG_735-3	Rd	Influenza A	16.01.2019	16.01.2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	390.AAG_735-1	Rd	Pneumonia	19.02.2019	19.02.2019	Grade3/Hospitalization	Unrelated	Dose continues unchanged
	463.AAG_735-3	Rd	Fever/ Arthralgia	10.07.209	10.07.209	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	525. AAG_735-1	Rd	Respìratory pneumonia	26.11.2019	26.11.2019	Grade3/Hospitalization	Unrelated	Temporary suspension of medication
	546.AAG_735-1	Rd	Pneumonia and renal failure	08.01.2020	08.01.2020	Grade3/Hospitalization	Unrelated	Temporary suspension of medication

CENTRE	SAE CODE	TREATMENT ARM	SAE DESCRIPTION	ONSET DATE SAE	END DATE SAE	SEVERITY	RELATION TO TREATMENT	OUTCOME
	558.AAG_735-3	Rd	Fever	04.03.2020	04.03.2020	Grade3	Unrelated	Temporary suspension of medication
	598. AAG_735-2	BiRd	Bilateral pneumonia due to COVID-19	11.02.2021	11.02.2021	Grade 4 - life-threatening /Hospitalization	Unrelated	Permanent discontinuation due to this adverse event
Marqués de Valdecilla University Hospital	377.AAG_736-03	BiRd	Renal failure	04.02.2019	04.02.2019	Grade3/Hospitalization	Likely to lenalidomide	Temporary suspension of medication
	404.AAG_736-1	Rd	Facial cellulitis secondary to folliculitis of the beard	15.03.2019	15.03.2019	Grade3/Hospitalization	Possibly to Lenamidomida and dexamethasome	Dose continues unchanged
	467.AAG_736-1	Rd	Fracture of the left external femoral condyle	16.07.2019	16.07.2019	Grade 3/Hospitalization-Persistent or significant disability or incapacity	Unrelated	Dose continues unchanged
Marqués de Valdecilla University Hospital	481.AAG_736-3	BiRd	Dysphagia	12.08.2019	12.08.2019	Grade3/Hospitalization	Likely to lenalidomide and unrelated to dexamerasona and clarithromycine	Permanent discontinuation due to this adverse event
	502.AAG_736-1	Rd	Respiratory infection	26.08.2019	26.08.2019	Grade 2 / Hospitalization	Unrelated	Temporary suspension of medication
SAS Jerez University Hospital	344.AAG_738-2	Rd	Fever	29.11.2018	29.11.2018	Grade3/Hospitalization	Unlikely to medication. Associated with infection	Temporary suspension of medication
CHUAC	368. AAG_739-1	BiRd	Upper respiratory infection	17.01.2019	17.01.2019	Grade3/Hospitalization	Unlikely	Temporary suspension of medication. Dosis of clarithromycine continues unchanged
	410.AAG_739-1	BiRd	Tremors	27.03.2019	27.03.2019	Grade 3/Persistent or significant disability or incapacity	UnLikely to study medication	Reduction of dexamethasome and Temporary suspension of clarithromycine
	425. AAG_739-1	BiRd	Pulmonary embolism	23.04.2019	23.04.2019	Grade3/Hospitalization	Likely to lenalidomide. Unlikely to dexamethasome and unrelated to clarithromycine.	Reduction of dexamethasome and Temporary suspension of clarithromycine
	478.AAG_739-1	BiRd	Myeloma progression	01.08.2019	Death	Death	NA	Permanent discontinuation due to this adverse event
	479.AAG_739-1	BiRd	Death	01.08.2019	Death	Death	NA	Permanent discontinuation due to this adverse event

Appendix 3: Main protocol deviations

CENTRE	NUMBER DEVIATION	DATE	DESCRIPTION
Salamanca University Hospital	1	29.03.2017	Patient 356-2: The following protocol-required tests were not determined for this patient: - There is no information on weight and height in the baseline examination section. - No blood tests have been performed for days 8, 15 and 22 of C1. - Quality of life C4. - There is no information on the evaluation of the response of C2. In addition, the values of the light chains in the evaluation of the C1 response, of the immunofixation in urine for cycles 2, 3, 4 and 5, and of the immunofixation in serum for this last cycle are not available. The monitor reminds us that these tests are essential to know the disease and to be able to monitor it. From the center, the SC comments that in the case of the evaluation of the C2 response, patient 356-2 did not carry the 24h urine. In addition, performing immunofixation in urine is not standard laboratory procedure.
Salamanca University Hospital	2	29.03.2017	Patient 356-3: The following protocol-required tests were not determined for this patient: - Dates of diagnosis of relevant diseases from the Patient's medical history. - There are no urine immunofixation values for cycles 1, 2 and 3, nor light chains in the evaluation of the response of cycles 2 and 3. The monitor reminds us that these tests are essential to know the disease and to be able to monitor it. From the center, the SC comments that urine immunofixation is not standard laboratory procedure.
Salamanca University Hospital	3	29.03.2017	Patient 356-5: The following protocol-required tests were not determined for this patient: - Dates of diagnosis of relevant diseases from the Patient's medical history. - Urine immunofixation values are not available for cycle 1 of treatment. The monitor reminds us that these tests are essential to know the disease and to be able to monitor it. From the center, the SC comments that urine immunofixation is not a standard laboratory procedure.
Salamanca University Hospital	4	04.10.2017	Patient 356-3: The following tests stipulated by protocol were not performed: Cycles 6 and 8 - Response evaluation: urine Immunofixation is not determined. Cycles 7 and 9 - Response evaluation: Neither urine immunofixation nor serum free light chains are determined.
Salamanca University Hospital	5	04.10.2017	Patient 356-9: The following tests stipulated by protocol were not performed: Screening - Baseline scan - Ejection Fraction not determined. Cycle 2 - Response evaluation - No urine CM determined.

Salamanca University Hospital	6	10.05.2018	Patient 356-2: The following test required by protocol is not determined for this Patient: - Urine Immunofixation value for cycle 7 is not available. The monitor reminds us that these tests are essential to know the disease and to be able to monitor it. From the center, the SC comments that urine immunofixation is not standard laboratory procedure.
Salamanca University Hospital	7	10.05.2018	Patient 356-3: For this Patient the following tests required by protocol are not determined: - Urine immunofixation values for cycles 4, 5 and 10-17.- Light chains in the evaluation of the response of cycles 4, 11 and 17. The monitor recalls that these tests are essential to know the disease and to be able to have a follow-up of the same. From the center, the SC comments that urine immunofixation is not a standard laboratory procedure.
Salamanca University Hospital	8	14.08.2018	Patient 356-5: The following tests required by protocol are not determined for this Patient: - Cycle 2, 8, 10, 12, 16 and 17 - Response evaluation: urine Immunofixation is not determined. - Cycle 4: - Response evaluation: Urine Immunofixation and oligoclonal bands are not determined. - Cycle 5, 6, 7, 9, 11 and 14 - Response evaluation: No determination of urine immunofixation and serum free light chains.
Salamanca University Hospital	9	14.08.2018	Patient 356-6: The following tests required by protocol are not determined for this Patient: - Cycle 1 - Response Evaluation: Immunofixation in serum and urine is not determined.
Salamanca University Hospital	10	14.08.2018	Patient 356-7: The following protocol-required tests are not determined for this Patient: - Cycle 3 and 4 - Response Evaluation: urine Immunofixation is not determined.
Salamanca University Hospital	11	26.02.2019	Patient 356-13: The following protocol-required tests are not determined for this Patient: - Cycle 2 and cycle 5 - Response evaluation: urine monoclonal component. - Cycle 3: - Response evaluation: Immunofixation in urine.
Salamanca University Hospital	12	26.02.2019	Patient 356-14: The following protocol-required tests are not determined for this Patient: - Cycle 1, Cycle 2 and Cycle 3 - Response Evaluation: urine monoclonal component.
Salamanca University Hospital	13	26.02.2019	Patient 356-16: The following protocol-required tests are not determined for this Patient: - Screening --Baseline scan: ejection fraction. --Bone assessment. --PET-CT. - Cycle 1 - quality of life.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Navarra Hospital Complex	1	42720	Evaluation of the response: For this Patient there is no information on CM in urine in C2. According to the Study Coordinator in the evaluation of the C2 response for Patient 341-1, CM in urine could not be performed because the Patient was hospitalised, with haematuria, and with a saline washout, so it was not possible to collect 24h urine as it would not be representative.
Navarra Hospital Complex	2	42720	Patient 341-2: The following deviations from protocol were detected during the monitoring visit: The required value in the eCRD of "SUV max" is not known. According to the Study Coordinator, the test performed was a CT scan, so this value will not be available. The serum CM value in the evaluation of the C2 response is unknown. According to the Study Coordinator, these tests were requested from the local laboratory, but were not analysed by the centre's local laboratory.
Navarra Hospital Complex	3	42944	Patient 341-3: Commercial Fortecortin 4 mg (8 tablets) is dispensed in error. Fortecortin 4 mg Lot: u0206; expiry 01/2020.
Navarra Hospital Complex	4	43081	Patient 341-1: The following tests stipulated by protocol were not performed: - Final Visit: No determination of CM in serum and urine.
Navarra Hospital Complex	5	43081	Patient 341-5: The following test stipulated by protocol was not performed: -Selection - Baseline scan: Ejection Fraction is not determined..
Navarra Hospital Complex	6	43081	Patient 341-6: The following test stipulated by protocol was not performed: -Selection -Disease at diagnosis: no determination of CM in urine.
Navarra Hospital Complex	7	43342	Patient 341-1: The Patient does not undergo the following tests stipulated by protocol: - Cycle 5: CM in serum and urine.
Navarra Hospital Complex	8	43342	Patient 341-2: The Patient does not undergo the following tests stipulated by protocol: - Cycle 2: Serum CM is not determined. - Cycle 8: Serum free light chains are not determined. - Cycle 19: Serum MC is not determined and the quality of life questionnaire is not performed. - Cycle 20: Serum free light chains are not determined.
Navarra Hospital Complex	9	43342	Patient 341-2: On day 1 of cycle 26 (August 14, 2018), Patient 341-2 is dispensed 56 tablets of Klacid® 500 mg lot 1088309; Cad. 08/2018. Said medication is not provided by the developer but is commercial medication.
Navarra Hospital Complex	10	43342	Patient 341-6: On day 1 of cycle 6 (March 7, 2018), Patient 341-6 is dispensed 4 vials of Fortecortin® 40mg, said dispensing format is outside of the study medication.

Navarra Hospital Complex	11	43342	Patient 341-10: On Day 1 of Cycle 1 (June 19, 2018), patient 341-10 is dispensed a bottle of Lenalidomide 10 mg lot 17F0061 which, as of the date of dispensing, was expired. The expiration date for that lot is 03/2018. Patient 341-10: On day 1 of Cycle 3 (August 14, 2018), patient 341-10 is dispensed 14 tablets of Klacid® 500 mg lot 1088309; Cad. 08/2020. That medication is not provided by the developer but is commercial medication.
Navarra Hospital Complex	12	43342	Patient 341-10: On 09/17/2018 the Pharmacy Service confirms via e-mail to the trial monitor that, to patient 341-10 in Cycle 1, the physician prescribed a dose of Fortecortin 40 mg in ampoules (each ampoule is 40mg/5ml).
Navarra Hospital Complex	13	43508	Patient 341-2: - Cycle 25: No ECOG is performed and CM is not determined in urine. - Cycle 26: No ECOG is performed and CM is not determined in urine. - Cycle 27: No ECOG is performed and MC is not determined in serum and urine. - Cycle 28: No ECOG or determination of MC in serum and urine. - Final Visit: No determination of MC in urine.
Navarra Hospital Complex	14	43508	Patient 341-4: - Selection: Ejection fraction is not determined.
Navarra Hospital Complex	15	43570	On February 25, the following containers were mistakenly destroyed along with the medication returned by the patient: - 1 container of Dexamethasome 8mg Lot E200900 Cad. 04/21. - 1 container of Klacid 500 mg Lot 1096991 Cad. 02/21
Navarra Hospital Complex	16	43570	Patient 341-4: - Cycles 19, 20, 21, 22, 23 and 25: Serum IF is not determined.
Navarra Hospital Complex	17	43570	Patient 341-5: - Cycle 1: Serum MC is not determined.
Navarra Hospital Complex	18	43570	Patient 341-6: - Cycle 3: Serum IF is not determined. - Cycle 5: Serum MC and urine MC are not determined. - Cycle 6: Serum MC is not determined. Final visit: Serum MC and vital signs are not determined.
Navarra Hospital Complex	19	43570	Patient 341-8: - Selection: Ejection fraction is not determined. - Cycle 1: CM in urine, CM in serum, oligoclonal bands and free light chains in serum are not determined. - Final visit: Vital signs, hematological and biochemical values are not determined. No determination of CM in urine, CM in serum, oligoclonal bands or serum free light chains.
Navarra Hospital Complex	20	43570	Patient 341-9: - Selection: Ejection fraction is not determined. - Cycle 1, 5, 6: CM in urine is not determined.
Navarra Hospital Complex	21	44081	Patient 341-11: On 07/09/2020 the pharmacist responsible for the study informed the CRA that on 20/08/2020 patient 341-11 was mistakenly prescribed lenalidomide 5mg instead of lenalidomide 10mg, which was prescribed by the researcher.

Navarra Hospital Complex	22	43746	The following tests are not determined: Patient 341-9: - Cycles 8 - Patient Status: ECOG Response Evaluation: Urine CM - Cycle 15- Response Evaluation: CM in urine. - Final Visit: ECOG. - Progression/Relapse: No date of response to salvage therapy is indicated.
Navarra Hospital Complex	23	43746	Patient 341-10: The following tests are not determined: - Screening - Baseline scan: ejection fraction. Baseline CBC: b2 microglobulin. - Cycles 2 to 7 - Patient Status: ECOG.
Navarra Hospital Complex	24	43746	Patient 341-11: The following tests are not determined: - Cycle 5 -Response assessment: serum CM. - Cycles 2 to 9 - Patient Status: ECOG.
Navarra Hospital Complex	25	44097	Patient 341-2: The following tests are not determined: - Cycles 26 and 27: Quality of life.
Navarra Hospital Complex	26	44097	Patient 341-6: The following tests are not determined: - Cycle 6: Quality of Life.
Navarra Hospital Complex	27	44097	The following tests are not determined: Patient 341-10: - Final visit- Final visit: vital signs. - Cycle 16- Response assessment: vital signs.
Navarra Hospital Complex	28	44097	The following tests are not determined: Patient 341-11: - Screening- Baseline scan: ejection fraction. - Cycle 15: Quality of life.
Navarra Hospital Complex	29	44246	The following test is not performed: Patient 341-6 - Selection: PEC CT

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
12 de Octubre University Hospital	1	23.02.2018	Patient 353-9: The Genetics Service informs that the marrow aspirate sample from the screening of Patient 353-9 is insufficient to perform a complete genetic study. Last October 18, 2017 a marrow aspirate was performed on this Patient with which she was diagnosed with myeloma and in this case a complete genetic study could be done. The doubt arises as to whether it would be possible to use these genetic results of 10/18/2017 to avoid repeating them again. The study coordinators, as of February 23, 2018, accept the previous results to avoid repeating the bone marrow aspirate.
12 de Octubre University Hospital	2	10.04.2017	Patient 353-6: This Patient who signed consent on 04/04/2017, meets all inclusion criteria and meets none of the exclusion criteria except for Creatinine clearance in the last two biochemistries. Values remain constant at 44 ml/min (cdk-epi), 45.62 ml/min (Cockcroft-gault), 40.35 ml/min/1.73m2 (Cockcroft-gault corrected for SC), 47.16 ml/min/1.73m2 (MDRD-4 IDMS). By means of this protocol deviation, the entry of this Patient into the study is requested since he meets all the other inclusion criteria and from the medical point of view is the best therapeutic alternative.
12 de Octubre University Hospital	3	10.07.2027	Patient 353-7: The patient who meets the inclusion criteria to be included in the study, presents symptomatic MM with 19% Plasma Cells and multiple lytic lesions seen on CT scan of May 26, 2017. Upon signing the IC and repeating an imaging test (X-Ray due to excessive CT delay time), those lesions are not seen. The medical team of the center considers that they are not seen because they are small (4mm) and are at the limit of detection of the technique. Dr. Mateos as I. Coordinator of the study, finally authorizes the inclusion of the patient.
12 de Octubre University Hospital	4	07.02.2018	Patient 353-10: The patient met the inclusion criteria to be included in the study. In this case, a bone marrow aspirate was performed approximately 2-3 weeks before the Informed Consent was signed. Thus, the center doubts whether this bone marrow aspirate would be valid. According to the study protocol, the bone marrow aspirate will be performed "within 4 weeks between the signing of the IC and the start of treatment". The monitor transfers this issue to the study coordinators who, on November 4, give their approval to include said Patient since they accept said test so that it does not have to be repeated. On February 9, 2018, Patient 353-10 signs the IC and begins the screening tests.
12 de Octubre University Hospital	5	05.12.2018	The following protocol-mandated tests were not performed: Patient 353-18: Signed ICF on November 19, 2018. It is agreed not to repeat the PET-CT again before starting treatment since the Patient has a PET-CT performed on November 8, 2018, it seems unnecessary to repeat the PET-CT and radiate said Patient in such a short time frame. The study coordination gives its approval to include the Patient accepting such test without the need to repeat it.

12 de Octubre University Hospital	6	26.09.2018	The following protocol-mandated tests were not performed: Patient 353-3: - Screening - Relevant medical history: failure to complete year of diagnosis for the following conditions: HTA and cervical osteoarthritis. - Cycle 2: - Patient Status: ECOG not determined. - Response Evaluation: Serum free light chains are not determined.
12 de Octubre University Hospital	7	26.09.2018	The following protocol-mandated tests were not performed: Patient 353-5: - Screening. - Baseline scan: Ejection fraction not determined. - Relevant medical history: Failure to complete the year of diagnosis of the following diseases: Benign prostatic hyperplasia and depressive symptomatology.
12 de Octubre University Hospital	8	11.04.2019	The following protocol-mandated tests were not performed: Patient 353-9: - Bone assessment: Patient does not have such assessment performed. - Disease at diagnosis: ECOG is not determined. - Cycle 10: Patient's vital signs are not taken. - Cycle 14: Patient's vital signs are not taken and serum free kappa light chain value is not determined. - Final visit: No ECOG or serum free kappa light chain value is determined.
12 de Octubre University Hospital	9	11.04.2019	The following tests stipulated by protocol were not performed: Patient 353-14: - Cycle 4: Response evaluation: no serum free kappa light chain determined. - Cycle 6: Patient does not complete the quality of life questionnaire.
12 de Octubre University Hospital	10	13.01.2020	The following protocol-mandated tests were not performed: Patient 353-5: - Cycle 1: Patient Status: ECOG. - Cycle 22: Response evaluation: Serum free light chains.
12 de Octubre University Hospital	11	13.01.2020	The following protocol-mandated tests were not performed: Patient 353-7: - Screening: Baseline scan: ejection fraction (%). - Selection: Bone assessment: no. of focal lesions. - Final visit: Final visit: ECOG. - Cycles 13, 17, 24 and 25: Patient Status: ECOG. - Cycles 20 and 24: Patient Status: Vital signs. - Cycles 10, 13, 16, 22: Response Evaluation: Serum Free Light Chains. - Cycle 23: Response Evaluation: Immunofixation in serum.
12 de Octubre University Hospital	12	13.01.2020	The following tests stipulated by protocol were not performed: Patient 353-14: Cycle 10: Response Evaluation: date of evaluation, serum CM, urine CM, Oligoclonal Bands and Serum Free Light Chains.

12 de Octubre University Hospital	13	13.01.2020	The following protocol-mandated tests were not performed: Patient 353-16: - Cycles 3, 4, 9 and 12: Patient Status: ECOG. - Cycles 4 and 9: Patient Status: Vital Signs. - Cycles 4, 6, 7 and 13: Response Evaluation: Serum Free Light Chains. - Cycle 5: Response Evaluation: CM in urine.
12 de Octubre University Hospital	14	13.01.2020	The following protocol-mandated tests were not performed: Patient 353-19: - Cycles 2, 3, 4, 4, 5, 6 and 7: Patient Status: ECOG. - Cycles 2, 4, 5, 6 and 7: Patient Status: Vital Signs. - Cycles 1, 2, 3, 3, 4, 6 and 7: Response Evaluation: Serum Free Light Chains. - Cycle 2: Response Evaluation: CM in urine.
12 de Octubre University Hospital	15	14.07.2020	The following protocol-mandated tests were not performed: Patient 353-10: - Selection - Baseline Scan: Ejection fraction (%). - Selection - PET-CT: Diagnostic imaging. PET-CT. - Cycle 3 - Response evaluation: Serum CM, Urine CM, Oligoclonal bands, Serum free light chains. - Cycle 8 - Evaluation of the response: Free kappa chains in serum. - Cycle 16 -Response evaluation: serum free light chains. Irregular cycle length: Cycle 14- starts on 6/03/2019 and response is evaluated on 28/03/2019. It has a duration of 22 days. Cycle 15- starts on 03/29/2019 and response is evaluated on 05/06/2019. It has a duration greater than 28 days.
12 de Octubre University Hospital	16	10.04.2023	The following tests stipulated by protocol were not performed: Patient 353-07: - Cycle 24: Response evaluation is not performed in this cycle.
12 de Octubre University Hospital	17	10.04.2023	The following protocol-mandated tests were not performed: Patient 353-10 At the screening visit the MO aspirate test is not performed, the results of this test are taken from Patient's previous visit to the center.
12 de Octubre University Hospital	18	10.04.2023	The following protocol-mandated tests were not performed: Patient 353-16: In cycle 17, in the assessment of the Patient's condition, the ECOG test was not performed.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Barcelona Clinic Hospital	1	24.10.2016	Patient 347-01 - Selection: In the relevant medical history section it is reflected that the Patient suffers from AHT but the date of diagnosis of said pathology is unknown. -In the section "plasmacytomas" the presence of plasmacytomas is reflected but their size is unknown. - Response evaluation: There is no data for immunofixation or free light chains in the evaluation of the C1 and C2 response. According to the protocol, such tests should be performed monthly until conventional Complete Response is achieved with two determinations. The monitor reports the importance of performing from now on this type of tests to know the evaluation of the response in each treatment cycle.
Barcelona Clinic Hospital	2	24.10.2016	Patient 347-02 The following protocol-marked tests are not performed: Response evaluation: Serum immunofixation: cycles 1, 3, 4, 9, 10, 10, 11, 12, 13, 14 and 15. Oligoclonal bands: cycles 1, 2 Free light chains in serum: cycles 1, 3, 4, 9, 10, 10, 11, 12, 13, 14 and 15
Barcelona Clinic Hospital	3	24.10.2016	Patient 347-04 According to the protocol, the vital signs, KPS, weight and height should be recorded in the evaluation before treatment; however, in the "baseline examination" selection section in the e-CRD, the Patient's height and weight values are not recorded. In the Patient's Medical History, it is verified that this information does not appear in the same. After consulting this fact with the Data Manager, the latter informs that if the data were not collected on that date prior to the first cycle, it will not be possible to obtain them.
Barcelona Clinic Hospital	4	13.12.2016	No samples have been sent for C2D21 for Patients 347-1, 347-2, 347-3 and 347-4. According to the protocol, Peripheral Blood and Serum should be sent at C2D21 (+7 days) to the reference laboratory for the immunophenotypic characterization of the Patient's immune status and to study the soluble components of the immune system, in order to detect the first changes in the Patient's immune system induced by the treatment. The Nursing Service commented that by mistake they did not send these samples and that they will take this cycle into account for the rest of the Patient when it corresponds to them.
Barcelona Clinic Hospital	5	10.05.2017	Patient 347-07 Patient would have had to start C4D1 on April 4 because she started C3D1 on 7/3/12. On 2/5/17 the +28 day delay in cycle initiation allowed by the trial was met but she was unable to initiate during that period because she was admitted to another center with Pneumonia that required IOT and ICU. After resolving the pneumonia she has presented various Aes that have prevented her from starting treatment (vertebroplasty for back pain, UTI and DVT) but once all the intercurrent processes were resolved we would like to restart treatment on 5/18/17. Patient has achieved a MBRP after 3 cycles of treatment in the clarithromycine, lenalidomide and dexamethasome arm.

Barcelona Clinic Hospital	6	09.06.2017	Patient 347-05 The following protocol-mandated tests were not performed: Screening - Baseline examination: Ejection Fraction is not determined - Relevant medical history: Year of diagnosis of the disease specified as "Paget's disease" is not known - Cycles 3, 4 and 7 - Response assessment: Urine MC (gr/24h) is not determined - Cycles 3, 4, 5, 6 and 7 - Response assessment: Free light chains (sFLC-κ and sFLC-λ) are not determined.
Barcelona Clinic Hospital	7	09.06.2017	Patient 347-11 The following test stipulated by protocol was not performed: Screening - Baseline Scan: Ejection Fraction is not determined.
Barcelona Clinic Hospital	8	07.02.2019	Patient 347-07 During the present monitoring visit, several deviations from the protocol were detected: - Screening - Baseline examination: Ejection Fraction is not determined - Cycle 1 - Response evaluation: Urine IF is not performed - Cycle 2 - The Patient does not complete the Quality of Life questionnaire - Cycle 3 - Response evaluation: Urine MC, serum IF and serum Free Light Chains are not determined - Cycle 4 - Response evaluation: Serum Free Light Chains are not determined - Cycle 4 - Response evaluation: Serum Free Light Chains are not determined - Cycle 4 - Response evaluation: Serum Free Light Chains are not determined - Cycle 4 - Response evaluation: Serum Free Light Chains are not determined. In addition, the Patient does not complete the Quality of Life questionnaire - Cycle 4 - Response evaluation: Serum Free Light Chains are not determined.
Barcelona Clinic Hospital	9	07.02.2019	Patient 347-09 During the present monitoring visit, several deviations from the protocol were detected: - Screening - Disease at diagnosis: urine CM is not determined. - Screening - Plasmacytomas: No indication of date, diagnostic test, cross-sectional size or axial size. - Cycles 1 and 2 - Patient does not complete Quality of Life questionnaire. - Cycle 3 - Response Evaluation: No urine IF or serum Free Light Chains are determined. In addition, the Patient does not complete the Quality of Life questionnaire. - Cycle 4 - Response Evaluation: Neither urine IF nor serum Free Light Chains are determined. In addition, the Patient does not complete the Quality of Life questionnaire. - Cycle 5 - Patient Status: ECOG is not determined. - Response Evaluation: No determination of urine IF or serum Free Light Chains. - Cycle 6 - Patient Status: ECOG is not determined. - Response Evaluation: No urine IF or serum Free Light Chains are determined. - Cycle 8 - Response Evaluation: No urine IF or serum Free Light Chains are determined.
Barcelona Clinic Hospital	10	07.02.2019	Patient 21 During the present monitoring visit, several deviations from the protocol were detected: - Screening - Baseline examination: Ejection fraction is not determined - Cycles 1, 2, 3, 4, 5, 6 and 7 - Response evaluation: Urine immunofixation and serum free light chains are not determined - Final visit - Response evaluation: Serum free light chains are not determined.
Barcelona Clinic Hospital	11	24/04/2019 - 25/04/2019	Patient 347-06 During the present monitoring visit, several deviations from the protocol were detected: - Selection - Baseline scan: Ejection fraction is not determined.

Barcelona Clinic Hospital	12	24/04/2019 - 25/04/2019	Patient 347-07 During the present monitoring visit, several deviations from the protocol were detected: - Cycles 5, 6 and 7 - Response evaluation: Serum Free Light Chains are not determined.
Barcelona Clinic Hospital	13	24/04/2019 - 25/04/2019	Patient 347-10 During the present monitoring visit, several deviations from the protocol were detected: - Selection - Baseline screening: No determination of Ejection Fraction - Cycles 1, 3, 4, 5, 7, 8 and 9 - Response evaluation: No determination of IF in urine or serum Free Light Chains. - Cycles 6 - Response evaluation: Serum Free Light Chains are not determined.
Barcelona Clinic Hospital	14	24/04/2019 - 25/04/2019	Patient 347-11 During the present monitoring visit, several deviations from the protocol were detected: - Selection - Baseline screening: No determination of ejection fraction - Cycles 1, and 2- Response evaluation: No determination of urine IF or oligoclonal bands. - Cycles 3, 4, 5, 6- Response evaluation: Urine IF is not determined.
Barcelona Clinic Hospital	15	24/04/2019 - 25/04/2019	Patient 347-15 During the present monitoring visit several deviations to the protocol are detected: - Screening - Baseline examination: No determination of Ejection Fraction - Cycle 1- Response evaluation: No determination of urine IF and oligoclonal bands - Final visit - Response evaluation: No determination of urine IF and oligoclonal bands.
Barcelona Clinic Hospital	16	24/04/2019 - 25/04/2019	Patient 347-08 During the present monitoring visit, several deviations to the protocol were detected: - Screening - Baseline examination: Ejection fraction is not determined - Cycle 1- Response evaluation: Serum free light chains are not determined - Cycle 1- Response evaluation: Serum free light chains are not determined. - Cycles 2, 3, 7, 8 and 9- Response evaluation: No determination of urine IF or serum free light chains.
Barcelona Clinic Hospital	17	17.02.2020	Patient 347-24 During the present monitoring visit several deviations to the protocol were detected: Selection - Plasmacytomas: No determination of transverse and axial size. Cycles 1, 2 and 7 - Response evaluation: Serum IF, Urine IF + Serum free light chains. Cycles 3, 5, 6, 8, 9 and 15 - Response evaluation: Serum free light chains.
Barcelona Clinic Hospital	18	21/07/2020 - 22/07/2020	Patient 347-18 During the present monitoring visit several deviations to the protocol were detected: Selection - Plasmacytomas: No determination of transverse and axial size. Cycles 1 to cycle 5, cycle 7, cycle 8 and cycles 10 to cycle 15 - Response assessment: IF urine, Oligoclonal bands + Free light chains in serum.
Barcelona Clinic Hospital	19	21/07/2020 - 22/07/2020	Patient 347-25 During the present monitoring visit, several deviations from the protocol were detected: Selection - Baseline scan: Ejection fraction.
Barcelona Clinic Hospital	20	21/07/2020 - 22/07/2020	Patient 347-27 During the present monitoring visit several deviations to the protocol are detected: Selection: PET CT Scan Progression/Relapse: MO aspirate Cycle 2 - Response assessment: Serum IF, oligoclonal bands and serum free light chains.

Barcelona Clinic Hospital	21	16/11/2020-17/11/2020	Patient 347-02 During the present monitoring visit several deviations to the protocol were detected: Response evaluation - Cycle 4 and 10: Serum IF + Serum Free Light Chains.
Barcelona Clinic Hospital	22	16/11/2020 - 17/11/2020	Patient 347-03 During the present monitoring visit several protocol deviations were detected: Response evaluation - Cycle 2, 5, 6 and 7: Serum IF Response evaluation - Cycle 9, 10 and 12: Serum IF and serum free light chains Final visit - Response evaluation: Serum IF + Serum free light chains Progression/Relapse: AMO
Barcelona Clinic Hospital	23	16/11/2020 - 17/11/2020	Patient 347-05 During the present monitoring visit several protocol deviations were detected: Response evaluation - Cycle 8, 10, 11 and 12: IF urine and serum free light chains. Response evaluation - Cycle 14, 15 and 20: Serum free light chains. Response evaluation - Cycle 18 and 21: IF serum, IF urine, oligoclonal bands and serum free light chains.
Barcelona Clinic Hospital	24	16/11/2020 - 17/11/2020	Patient 347-29 During the present monitoring visit, several deviations from the protocol were detected: Screening - Baseline examination: Ejection fraction Screening - Bone assessment.
Barcelona Clinic Hospital	25	16/11/2020 - 17/11/2020	Patient 347-30 During the present monitoring visit several deviations to the protocol were detected: Screening - Bone assessment - Diagnostic imaging + bone series. Response evaluation - Cycle 10: Serum free light chains.
Barcelona Clinic Hospital	26	11.08.2021	Patient 347-05 During the present monitoring visit several deviations to the protocol were detected: Response evaluation - Cycles 22, 23, 24, 26, 27 and 30: Serum free light chains. Response evaluation - Cycles 25, 28, 29, 31 and 32: Serum IF, urine IF, oligoclonal bands and serum free light chains.
Barcelona Clinic Hospital	27	11.08.2021	Patient 347-20 During the present monitoring visit several deviations to the protocol were detected: - Response evaluation - Cycles 2, 3, 4, 5 and 7: Serum free light chains. - Response evaluation - Cycles 9, 13, 16, 18: Urine IF and oligoclonal bands. - Response evaluation - Cycle 25: CM urine, IF urine, oligoclonal bands and serum free light chains. - Response evaluation - Cycles 8, 10-12, 14-15, 17, 19-24, 26-31: urine IF, oligoclonal bands and serum free light chains.
Barcelona Clinic Hospital	28	11.08.2021	Patient 347-30 During the present monitoring visit, several protocol deviations were detected: - Response evaluation - Cycle 1: Urine IF. - Response evaluation - Cycles 9, 10 and 16: Serum free light chains. - Response evaluation - Cycles 2-4, 6 and 11: CM urine, IF urine, oligoclonal bands and serum free light chains. - Response evaluation - Cycles 5, 7-8, 12, 15 and 17: Urine IF, oligoclonal bands and serum free light chains.

Barcelona Clinic Hospital	29	31.01.2022	On 01/31/2022 the Pharmacy Service notified the study monitor that a bottle of lenalidomide 25mg belonging to the GEM-CLARIDEX trial had been dispensed in error to a Patient from another clinical trial, GEM2017FIT. The dispensed kit was No. 2964514, from lot 20F0149. The error was detected at the time of recording the return of the container at the end of the cycle. As a result, the package will be set aside with the rest of the returns of the Patients of the GEM2017FIT trial, and will be removed from the available stock in the Fundanet records of the GEM-CLARIDEX trial.
Barcelona Clinic Hospital	30	05.04.2022	Patient 347-20 On 03/29/2022 the Pharmacy Service informed the study monitor that, at the start of Cycle 47 of treatment on 03/17/2022, a bottle of lenalidomide 25mg (kit no. 2964520, Lot 20F0149) was dispensed in error to Patient 347-20, instead of the prescribed lenalidomide 15mg. By the time the error was detected (3/28/2022), Patient had taken 12 capsules of lenalidomide 25mg. Given that the Patient had not suffered any Adverse Event nor had she shown signs of toxicity, the Pharmacy Service, after consultation with the responsible PI, summoned the Patient on 03/30/2022 to withdraw the container of lenalidomide 25mg and dispense a container of lenalidomide 15mg (kit no. 2055486, Lot 21F0256), which the Patient will take until the end of this treatment cycle. All these facts were communicated on 03/29/2022 to the Study Coordinators (Dr. Mateos and Dr. Puig), who, taking into account the reason for the lenalidomide dose reduction (Asthenia), the error (lenalidomide administration at a higher dose than the one she was taking, but not toxic) and that it has not had any serious consequence for the Patient, have considered it a major deviation, not serious, which is exposed in this form.
Barcelona Clinic Hospital	31	11.08.2022	Patient 347-06 During the current monitoring visit, several deviations from the protocol were detected: Patient status: cycles: 14-25 ECOG
Barcelona Clinic Hospital	32	18.08.2022	Patient 347-24 During the present monitoring visit, several deviations from the protocol were detected: evaluation of the response cycle 7, 11 immunofixation cycle 19, 23 chain quantification
Barcelona Clinic Hospital	33	11.08.2022	Patient 347-20 During the present monitoring visit, several deviations from the protocol were detected: evaluation of the response - cycles 8,12 urine immunofixation - cycles 31-50 urine immunofixation and bands
Barcelona Clinic Hospital	34	11.08.2022	Patient 347-14 During the present monitoring visit, several deviations from the protocol were detected: evaluation of the response - cycle 7, 11 immunofixation - cycle 19, 23 chain quantification

Barcelona Clinic Hospital	35	28.04.2023	Patient 347-01 During the present monitoring visit, several deviations to the protocol were detected: - Response evaluation: Urine immunofixation cycles 1, 2, 3, 4, 5, 6, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16. Free chains in serum cycles 1, 2, 3, 3, 4, 8, 9, 10, 10, 11, 12, 13, 14, 15, 16
Barcelona Clinic Hospital	36	27.04.2023	Patient 347-02 The following protocol-marked tests are not performed: Response evaluation: Serum immunofixation: cycles 1, 3, 4, 9, 10, 10, 11, 12, 13, 14 and 15. Oligoclonal bands: cycles 1, 2 Free light chains in serum: cycles 1, 3, 4, 9, 10, 10, 11, 12, 13, 14 and 15
Barcelona Clinic Hospital	37	27.04.2023	Patient 347-04 The following protocol-marked tests are not performed: Response evaluation CM serum: cycles 1, CM urine: cycles 1, Immunofixation in serum: cycles 1, 11, 12 Immunofixation in urine: cycles 1 , 11, 12 Oligoclonal bands: cycles 1 Free light chains in serum: cycles 1, 12, 13, 14, 15
Barcelona Clinic Hospital	38	27.04.2023	Patient 347-05 The following tests stipulated by protocol were not performed: Response evaluation CM in urine: cycles 1, 2, 3, 3, 4, 7 Serum immunofixation: cycle 18 Immunofixation in urine: cycles 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 16, 17, 18 Oligoclonal bands: cycles 13, 16, 17, 18 Free light chains in serum: cycles 1, 2, 3, 4, 5, 6, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14, 15, 16, 17, 18, 18, 19
Barcelona Clinic Hospital	39	19.10.2023	Patient 347-05 The following tests stipulated by protocol were not performed: - Response evaluation: light chains of cycles 6, 7, 8 and 13.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Virgen de las Nieves Hospital	1	30.06.2016	Patient 359-1: During the monitoring visit made to the center last August 03, 2016, the following deviations to the protocol are detected: - According to the study protocol, within four weeks prior to the start of treatment a whole body Positron Emission Tomography/CT Scan (PET/CT) should be performed. Patient having been included on April 21, 2016, the test performed on February 19, 2016 is included in the e-CRD, although this test is not performed within four weeks prior to treatment. - The blood sample corresponding to C2D21 for this Patient is not sent to the assigned reference laboratory (CIMA) as specified in the protocol.
Virgen de las Nieves Hospital	2	30.06.2016	Patient 359-3: During the monitoring visit made to the center last August 03, 2016, the following deviations to the protocol are detected: - According to the study protocol, within four weeks prior to the start of treatment a whole body Positron Emission Tomography/CT Scan (PET/CT) should be performed. Patient having been included on June 2, 2016, the test performed on April 19, 2016 is included in the e-CRD, although this test is not performed within four weeks prior to treatment. - According to the study protocol, Patient should take dexamethasome 20mg/day on days 1, 8, 15 and 22 of each cycle. During the first treatment cycle and at medical discretion the Patient took 40mg/day on days 1, 8, 15 and 22.
Virgen de las Nieves Hospital	3	25.11.2016	Patient 359-5: This Patient signed the C1 on Nov 21, yesterday Nov 24 the molecular study was performed and is scheduled to start treatment on Thursday Dec 1. On the 10 Nov blood test he has a strictly noraml creatinine (0.62) with Cr Cl of 63 ml/min. However, in the analysis of yesterday 24th (which is the valid one after signing) he has 1.03, which with the weight of 54 kg gives a Cr Cl of approx. 38. I request permission to start treatment, since all other criteria are ok and I believe it is the best therapeutic alternative for the Patient.
Virgen de las Nieves Hospital	4	15.02.2017	Patient 359-1: Immunofixation in urine is not performed in the evaluation of the response of cycle 6, 7 and 8. According to the laboratory, the quantification of this value should not be performed since, according to the center's The laboratory indicates that the quantification of this value is not appropriate since it is not performed according to the usual procedure of the center, since the quotient of free light chains in serum is not pathological. According to the protocol, immunofixation in serum and urine should be performed at the beginning of each cycle to evaluate the response of the previous cycle.
Virgen de las Nieves Hospital	5	15.02.2017	Patient 359-4: Immunofixation in urine is not performed in the evaluation of the response of cycles 2 and 3. According to the laboratory, this is not the usual procedure in the center since the serum free light chain ratio is not pathological. According to the protocol, immunofixation in serum and urine should be done at the beginning of each cycle to evaluate the response of the previous cycle..

Virgen de las Nieves Hospital	6	08.08.2018	General: According to the study protocol, the quality of life questionnaires should be carried out at screening (<14 days before the start date), on D1C1 and on D1 of the remaining cycles. However, in this center the one corresponding to the time of selection was not carried out and therefore the information from the forms corresponding to the following cycle was entered in the eCRD. As the forms are completed at the end of each cycle, the information from each of the completed life questionnaires actually corresponds to the information that should be completed at the beginning of the following cycle.
Virgen de las Nieves Hospital	7	28.11.2018	Patient 359-3 Immunofixation in serum is not performed in the evaluation of the response of cycle 11. According to the laboratory, due to "insufficient sample volume". In addition, oligoclonal bands are not quantified in this cycle. Immunofixation in urine is not performed in the evaluation of the response of cycle 17 and 23. According to the laboratory, in cycle 17 "it does not receive the urine sample 24 hours". According to the protocol, serum and urine immunofixation should be done at the beginning of each cycle to evaluate the response of the previous cycle.
Virgen de las Nieves Hospital	8	31.07.2019	Patient 359-7: Cycle 6 - Response evaluation: Urine immunofixation is not determined. According to the laboratory because "not applicable since 24-hour urine FLC values are normal". Cycle 7 - Response evaluation: No urine MC is determined. According to the laboratory because "not applicable as 24-hour urine FLC values are normal". Cycle 9 - Response evaluation: No urine MC determined. Cycle 10 - Response evaluation: Not performed due to exitus. Final visit - Response evaluation: Not performed due to exitus.
Virgen de las Nieves Hospital	9	31.07.2019	Patient 359-10: - Cycle 5, Cycle 12 and Final Visit - Response evaluation: Urine immunofixation is not determined.
Virgen de las Nieves Hospital	10	11.09.2020	Patient 359-1: The following tests stipulated by protocol were not performed: - Cycle 30: Patient Status: ECOG. - Cycles 8, 12, 16, 26, 38, 39, 42, 44, 51 and 55: Response evaluation: Immunofixation in urine.
Virgen de las Nieves Hospital	11	11.09.2020	The following tests stipulated by protocol were not performed: Patient 359-4: - Final Visit: Response Evaluation: Serum Immunofixation. - Cycles 24 and 25: Patient Status: ECOG. - Cycles 3, 15, 36, 37 and 38: Response Evaluation: Urine Immunofixation. - Cycles 43 and 47: Response Evaluation: Serum Immunofixation. - Cycle 46: Response evaluation: Immunofixation in serum and urine.

Virgen de las Nieves Hospital	12	11.09.2020	The following tests required by the protocol were not performed: Patient 359-6: - Cycles 8 and 9: Response evaluation: urine immunofixation. - Cycle 10: Response evaluation: Serum immunofixation. - Cycle 11: Response evaluation: serum CM, oligoclonal bands and serum free light chains.
Virgen de las Nieves Hospital	13	11.09.2020	The following protocol-mandated tests were not performed: Patient 359-11: - Cycle 15: Patient Status: ECOG. - Cycles 2, 9, 11, 13, 14 and 15: Response evaluation: Immunofixation in urine.
Virgen de las Nieves Hospital	14	22.12.2020	The following protocol-mandated tests were not performed: Patient 359-8: - Screening: Baseline scan: ejection fraction (%). - Cycles 5 and 30: Patient Status: ECOG. - Cycles 14, 17, 27 and 30: Response evaluation: Urine immunofixation. - Cycle 14: Quality of life.
Virgen de las Nieves Hospital	15	22.12.2020	The following protocol-mandated tests were not performed: Patient 359-12: - Screening: PET-CT. - Cycle 11: Patient Status: ECOG. - Cycles 10 and 12: Response evaluation: Immunofixation in urine. - Cycle 14: Response Evaluation: Urine CM. - Cycle 11: Quality of Life.
Virgen de las Nieves Hospital	16	25.05.2021	The following tests stipulated by protocol were not performed: Patient 359-1: Final visit - Response evaluation: IF in urine.
Virgen de las Nieves Hospital	17	25.05.2021	The following tests stipulated by protocol were not performed: Patient 359-13: Cycle 23 - Response evaluation: serum CM and serum free light chains.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Virgen de la Victoria Hospital	1	01.02.2017	Patient 343-1 and 343-2: There is no information in the relevant medical history of both Patients about the dates of diagnosis of the disease. . According to the protocol, during the screening period, the medical history of all the included Patients must be known. The Study Coodinator comments that it is complicated to know the dates when the events occurred in another hospital and are not reflected in the current history.
Virgen de la Victoria Hospital	2	26.07.2017	Patient 343-3: On 07/26/17 (D1C6 of Rd-arm1 treatment) the Patient included in the trial had an absolute neutrophil count (ANC) of 700/ mm3 and was treated at the same dose as in previous cycles (lenalidomide 25 mg/day x 21 days and dexamethasome 20 mg/day x 4 days) and GCSF 30 mill IU SC was added on Mondays and Thursdays of this cycle. According to the protocol for the initiation of a new cycle, a RAN equal to or greater than 750/mm3 is required and if this is not the case, it should be evaluated in 1 week and reinitiate once this figure is reached. After detecting the deviation from the protocol on 08/03/17, an appointment was made for 08/09/17 to check the neutrophil count.
Virgen de la Victoria Hospital	3	23.04.2018	Patient 343-8: The Patient was included in the trial on April 16, 2018, a PET/CT scan is requested (pending appointment, at least it will take a few days or weeks), but he already has a bone map done on March 26, 2018 and a CT scan on April 23, 2018. These dates are prior to Patient's inclusion in the trial, so the doubt arises as to whether these imaging tests (bone map and CT scan) would be valid to start treatment or, on the contrary, it would be necessary to wait for the PET/CT results to start treatment. The center indicates that they do not want to delay the start of treatment too much because the Patient has moderate renal insufficiency. The monitor transfers the doubt to the study coordinators who, as of April 23, 2018, indicate that these tests are valid (especially the CT scan) for the Patient to start treatment.
Virgen de la Victoria Hospital	4	27.04.2018	The study protocol specifies the following as exclusion criteria: "The patient has active bacterial or viral infections, or any coexisting medical problem that would significantly increase the risks of receiving this treatment regimen. According to Dr. Garcia, the study treatment was scheduled to begin today, however, an infection has been confirmed based on the urinalysis performed. The culture was positive for Klebsiella although Patient is doing well clinically. Dr. Garcia asks if, due to this infection, the start of treatment should be delayed or if an exception to the protocol can be made to start as soon as possible. The monitor transfers the doubt to the study coordinators who, as of April 27, 2018, indicate that it would be advisable to wait at least 48 or 72 hours to confirm that the infection is controlled before starting treatment because of the danger of it turning into sepsis.
Virgen de la Victoria Hospital	5	09.05.2017	Patient 343-5: The Patient is taking Dabigatran as an anticoagulant due to atrial fibrillation. Given that the Patients at the start of the trial have to receive anticoagulant treatment with Adiro, heparin or antivitamin K, Dr. Garcia asks if Dabigatran is allowed as prophylaxis for TVE during the clinical trial. The monitor transfers the query to the study coordinators who, as of May 9, 2017, allow this exception to the protocol so that the Patient can continue with his usual prophylaxis.

Virgen de la Victoria Hospital	6	23.03.2021	The following protocol-mandated tests were not performed: Patient 343-1: Cycle 25: Response Evaluation. Urine CM is not counted.
Virgen de la Victoria Hospital	7	23.03.2021	The following protocol-mandated tests were not performed: Patient 343-2: Cycle 36: Quality of Life. No patient questionnaire was performed.
Virgen de la Victoria Hospital	8	29.07.2021	The following protocol-mandated tests were not performed: Patient 343-6: Cycles 33 and 37: Patient Status - ECOG.
Virgen de la Victoria Hospital	9	29.07.2021	The following tests stipulated by protocol were not performed: Patient 343-14: - Cycles 13 and 17: Patient Status - ECOG. - Cycles 21 to 27: Response Evaluation - No urine CM counted.
Virgen de la Victoria Hospital	10	22.03.2023	Patient 343-14: Quality of life questionnaire is not carried out in cycles 42, 43, 49, 50
Virgen de la Victoria Hospital	11	22.03.2023	Patient 343-6: - Response assessment: No serum CM quantification in cycle 2 – - No quality of life questionnaire in cycles 62 and 70

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Costa del Sol Hospital	1	23.02.2017	Patient 342-4: The following deviations from protocol were detected. - Sending of samples: The Bone Marrow sample corresponding to the screening for Patient 342-4 was not sent to the assigned reference laboratory (H. 12 de Octubre), as specified in the protocol. Prior to the Patient's inclusion in the study, the center consulted the Patient's entry since the AMO was dry due to marrow packing, which occurs in some cases when there is a lot of disease. The Coordinating Investigators of the study were consulted and accepted the inclusion of this Patient.
Costa del Sol Hospital	2	23.02.2017	General: The following protocol deviations were detected: - Corrected Calcium in Basal Analysis: For none of the Patients included in the study so far (342-1, 342-2, 342-3 and 342-4) the value of Corrected Calcium in the "Basal Analysis" section corresponding to the screening of the Patients is available as indicated in the protocol. The Study Coodinator comments that the laboratory does not provide this value as such, since they provide the Total Calcium.
Costa del Sol Hospital	3	22.03.2018	Patient 342-1: The following tests stipulated by protocol were not performed: Cycle 2 - Response evaluation: urine monoclonal component. Final Visit - Response Evaluation: Urine Monoclonal Component.
Costa del Sol Hospital	4	22.03.2018	The following tests stipulated by protocol were not performed: Patient 342-2: - Final visit - Plasmacytomas: axial size not determined. - Final visit: ECOG.
Costa del Sol Hospital	5	20.11.2019	The following tests stipulated by protocol were not performed: Patient 342 6: - Cycle 12 - Response Evaluation: urine CM and urine Immunofixation. - Cycle 18 - Patient Status: ECOG. - Cycle 19 - Patient Status: ECOG. - Cycle 24 - Response Evaluation: Serum CM, Serum Immunofixation, serum kappa free chains and serum lambda free chains. - Cycle 31 - Patient Status: ECOG.
Costa del Sol Hospital	6	20.11.2019	The following tests stipulated by protocol were not performed: Patient 342-2: Cycle 9 - Quality of life: questionnaire.
Costa del Sol Hospital	7	20.11.2019	The following protocol-mandated tests were not performed: Patient 342-4: Cycle 6 - Quality of life: questionnaire.
Costa del Sol Hospital	8	15.07.2020	The following protocol-mandated tests were not performed: Patient 342-3: Final Visit: Final Visit: ECOG.
Costa del Sol Hospital	9	15.07.2020	The following protocol-mandated tests were not performed: Patient 342-5: - Final visit: Response evaluation: CM in urine and serum free light chains. - Cycle 1: Response evaluation: CM in urine and serum free light chains.

Costa del Sol Hospital	10	15.07.2020	The following protocol-mandated tests were not performed: Patient 342-4: - Cycle 17: Response evaluation: CM in urine. - Cycle 34: Response evaluation: CM in urine and serum free light chains. - Cycle 40: Response evaluation: CM in serum.
Costa del Sol Hospital	11	30.11.2020	The following protocol-mandated tests were not performed: Patient 342-3: - Cycle 6: Quality of life. - Cycle 12: Quality of life. - Cycle 40: Quality of life.
Costa del Sol Hospital	12	30.11.2020	The following protocol-mandated tests were not performed: Patient 342-4: Cycles 17, 20, 26, 26, 28-44: Quality of life.
Costa del Sol Hospital	13	30.11.2020	The following protocol-mandated tests were not performed: Patient 342-6: - Cycle 41: Patient Status - ECOG. - Cycles 2 and 18-44: Quality of Life.
Costa del Sol Hospital	14	09.07.2021	The following protocol-mandated tests were not performed: Patient 342-6: Cycles 44-51: Quality of Life
Costa del Sol Hospital	15	01.08.2022	The following protocol-mandated tests were not performed: Patient 342-6: - Quality of Life Cycle 51-65
Costa del Sol Hospital	16	21.03.2023	The following protocol-mandated tests were not performed: Patient 342-6: - Quality of Life questionnaires in Cycles 66 - 73 were not performed.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Virgen de Valme Hospital	1	19.12.2016	<u>Patient 352 -1</u> Evaluation of the response: As reported by the Study Coordinator in the evaluation of the response of cycles 1 and 2 for this Patient, Immunofixation in urine was not performed. The monitor reports the importance of performing from now on this type of test to know the evaluation of the response in each treatment cycle and the Study Coordinator is committed to perform such measurement in future evaluations. Sending of biological samples: The biological samples corresponding to C2D21 stipulated by protocol were not sent. The Study Coordinator comments that it was a planning error and that it will be taken into account for future Patients to be included. Informed consent: The HIP+CI approved on October 24 by the CEIC of Reference (H. de Salamanca) is not provided to the Patient. The Study Coordinator undertakes to provide this document at the Patient's next visit.
Virgen de Valme Hospital	2	23.11.2017	<u>Patient 352-1:</u> - Cycle 3 and cycle 4 - Response evaluation: No urine CM determined. - Cycle 7: Response evaluation is not determined. Only the routine blood test is available since by mistake the proteinogram was not extracted. - Cycle 8 - Response evaluation: CM in urine and free light chains in serum are not determined. - Cycle 9 - Response evaluation: No determination of CM in urine and oligoclonal bands. - Final visit - Response evaluation: No determination of urine MC and oligoclonal bands. - Quality of life: At the beginning of cycles 7 and 9 the Patient is not asked to complete the quality of life questionnaires.
Virgen de Valme Hospital	3	13.03.2019	<u>Patient 352- 7:</u> - Screening - Baseline examination - Ejection fraction is not determined. - Cycle 2 - Response Evaluation - No determination of CM in urine. - Cycle 2 - Response Evaluation - No serum Free Light Chains determined. - Cycle 4 - Response Evaluation - No determination of CM in urine. - Cycle 6 - Response Evaluation - No determination of CM in urine. - Cycle 7 - Response Evaluation - No urine MC determined. - Final Visit - Response Evaluation - No serum Free Light Chains determined. - Final Visit - Response Evaluation - No urine MC determined.

Virgen de Valme Hospital	4	13.03.2019	Patient 352-8: - Screening - Baseline examination - No determination of CM in urine. CM in urine is not determined. - Screening - Baseline examination - Ejection fraction is not determined. - Cycle 1 - Response Evaluation - No urine MC or serum free light chains determined. Free light chains in serum. - Cycle 2 - Response Evaluation - No determination of urine MC. - Cycle 3 - Response Evaluation - No determination of MC in urine or serum free light chains. Free light chains in serum. - Cycle 4 - Patient Status - No determination of ECOG or urine MC. - Cycle 5 - Patient Status - ECOG is not determined. - Cycle 5 - Response Evaluation - No determination of urine MC, serum MC and serum free light chains. serum and serum free light chains are not determined. - Cycle 6 - Response Evaluation - No determination of urine MC. - Cycle 7 - Response Evaluation - No determination of MC in urine and serum free light chains. Serum free light chains. - Final Visit - Response Evaluation - No urine MC or serum free light chains determined. Serum free light chains.
Virgen de Valme Hospital	5	25.10.2018	Patient 352-2: - Selection - Baseline scan - Ejection fraction is not determined.
Virgen de Valme Hospital	6	25.10.2018	The following protocol-mandated tests were not performed: Patient 352-5: - Screening - Baseline scan - Ejection fraction. - Bone assessment: Diagnostic imaging. MRI. - Cycle 2 - Response evaluation: No determination of CM in urine.
Virgen de Valme Hospital	7	25.10.2018	Patient 352-10: Cycle 1 and cycle 2 - Response assessment: No determination of MC in urine.
Virgen de Valme Hospital	8	05.07.2018	Patient 352- 4: Screening: The following protocol-specified tests are not performed: Bone assessment, PET-CT and MO Aspirate.
Virgen de Valme Hospital	9	22.10.2019	The following protocol-mandated tests were not performed: Patient 352-6: - Screening - Relevant medical history - Diagnostic year of disease. - Cycle 1 - Response Evaluation - Urine CM, Oligoclonal Bands and Serum Free Light Chains. - Cycle 2 - Response Evaluation - CM in urine, Oligoclonal bands and Serum free light chains. - Cycle 3 - Response Evaluation - CM in urine. - Cycle 4 - Response Evaluation - CM in urine. - Cycle 5 - Response Evaluation - CM in urine and Serum Free Light Chains. - Cycle 6 - Patient Status - ECOG. - Cycle 6 - Response Evaluation - CM in urine and Serum Free Light Chains. - Cycle 7 - Response Evaluation - CM in urine and Serum Free Light Chains. - Cycle 8 - Response Evaluation - CM in urine. - Cycle 9 - Response Evaluation - CM in urine and Serum Free Light Chains. - Cycle 12 - Response Evaluation - CM in urine.

Virgen de Valme Hospital	10	22.10.2019	The following protocol-mandated tests were not performed: Patient 352-10: - Screening - Disease at diagnosis - CM in urine. - Cycle 1 - Response Evaluation -CM in urine. - Cycle 4 - Response Evaluation -CM in urine. - Cycle 5 - Response Evaluation - CM in urine and serum free light chains. - Cycle 7 - Response Evaluation - CM in urine. - Cycle 8 - Response Evaluation - CM in urine. - Cycle 10 - Response Evaluation - CM in serum. - Cycle 11 - Response Evaluation - CM in serum and CM in urine.
Virgen de Valme Hospital	11	25.02.2020	The following tests were not performed stipulated by protocol: Patient 352-1: Cycle 8- Response Evaluation: CM in urine and Free Light Chains in serum. in serum.
Virgen de Valme Hospital	12	25.02.2020	The following protocol-mandated tests were not performed: Patient 352-2: - Screening - Plasmacytomas: date of evaluation and transverse and axial size unknown due to The CT scan was performed at a private center and data is unknown. - Final Visit - Response evaluation: CM in urine. - Cycles 1, 2, 6 - Response Evaluation: Serum CM, Urine CM and Oligoclonal Bands. - Cycle 4 - Response evaluation: CM in serum and CM in urine. - Cycle 5 - Response evaluation: CM in urine. - Cycle 6 - Response evaluation: not evaluated due to confirmation of disease progression in the previous cycle.
Virgen de Valme Hospital	13	25.02.2020	Patient 352-4: - Selection - Disease at diagnosis: no urine CM. CM is not evaluated in urine. - Final Visit - Plasmacytomas, Final Visit and Response Evaluation: not evaluated by Patient's Exitus. - Cycle 1 - Response Evaluation: not evaluated by Patient's Exitus.
Virgen de Valme Hospital	14	25/02/2020	Patient 352-5: - Final Visit - Evaluation of the response: the response is not evaluated. - Cycle 1 - Evaluation of the response: the response is not evaluated because it is not requested by mistake.
Virgen de Valme Hospital	15	25.02.2020	Patient 352-6 - Selection - Disease at diagnosis: no urine MC is assessed.
Virgen de Valme Hospital	16	25.02.2020	The following tests stipulated by protocol were not performed: Patient 352-10 - Cycle 3 - Response Evaluation - CM in urine, Oligoclonal Bands and Free Light Chains in serum (hemolyzed serum). - Cycles 6 and 13 - Response Evaluation - CM in urine. - Cycle 12 - Response Evaluation - CM in urine and Serum Free Light Chains.

Virgen de Valme Hospital	17	29.07.2020	The following protocol-mandated tests were not performed: <u>Patient 352-6:</u> - Screening: Bone evaluation: Diagnostic imaging. MRI. - Cycle 5: Patient Status: ECOG. - V. Final: Response evaluation: CM in urine. - Progression/Reclapse: M.O. Aspirate. - Cycle 11: Response evaluation: CM in urine, Free light chains in serum. - Cycle 13: Response evaluation: not evaluated due to confirmation of previous progression at the end of the cycle. - Cycles 2 and 13: Quality of life: the forms have not been completed.
Virgen de Valme Hospital	18	29.07.2020	The following protocol-mandated tests were not performed: <u>Patient 352-7:</u> - Cycle 1: Patient Status: ECOG. - Cycles 1 and 5: Quality of life: forms not performed. - Progression/Relapse: M.O. Aspirate.
Virgen de Valme Hospital	19	29.07.2020	<u>Patient 352-8:</u> – Cycles 2 and 4: Quality of life: no forms have been completed.
Virgen de Valme Hospital	20	21.11.2022	<u>Patient 352-08:</u> - Selection: bone marrow aspirate is performed but the sample is diluted and not suitable for diagnosis. - Cycle 2: the quality of life questionnaire is not available for monitoring at the center, as it has been misplaced for years, so there is no possibility of verifying the data.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Cabueñes Hospital	1	30.06.2016	Patient 348-1: According to the study protocol, the Patient should take dexamethasome 40mg per day on days 1, 8, 15 and 22 of each cycle. Dr. Gonzalez confirms to the monitor that in the first treatment cycle the Patient was dispensed one bottle of dexamethasome 4mg. The monitor detects during this monitoring visit that with only one bottle of dexamethasome 4mg and since no further medication was dispensed during the first cycle, it is not possible to achieve the dosage necessary to cover the Patient's treatment for the entire cycle. As described above, the Patient did not take during the first treatment cycle the sufficient dose of dexamethasome described in the study protocol.
Cabueñes Hospital	2	30.06.2016	Patient 348-2: The following tests/determinations were not performed as specified in the study protocol: - Screening: quantification of β2 Microglobulin was not performed at baseline CBC. - Medication: Dr. Gonzalez confirms to the monitor that for cycle 1 instead of dispensing clarithromycin from the study, commercial medication was dispensed outside the Clinical Trials Pharmacy Service of the center, where indeed such dispensing was not registered. Nevertheless, the Patient did correctly receive the treatment established in the study protocol. - Medication: Dr. Gonzalez confirms to the monitor that during the first 5 treatment cycles dexamethasome 8mg was dispensed to the Patient. According to the study protocol, during the aforementioned cycles the Patient should have taken dexamethasome 20mg. The Principal Investigator confirms according to the returned medication return, that the Patient took only 16 mg on the indicated days.
Cabueñes Hospital	3	17.05.2017	Patient 348-1: In cycle 1, serum free light chains have not been analysed in the response assessment section.. Patient 348-2: In cycles 1, 3 and 8, serum free light chains have not been analysed in the response evaluation section. Patient 348-5: Ejection fraction has not been measured in the baseline scanning section during screening.
Cabueñes Hospital	4	16.03.2018	Patient 348-23: Patient to be dispensed Lenalidomide 10 mg 21 capsules (Batch 17F0061 Cad. 03/2018 ID 4128817) to cycle from March 7 through March 27. In error Lenalidomide 10 mg, 21 capsules are dispensed. Lot 17F0061 Cad.03/2018 ID 4128904 of protocol R2-GDP-GOTEL promoter: Oncology group for the treatment and study of lymphomas (GOTEL). Today 16/3/2018, the error is noticed and Patient is telephoned at home. He went to the hospital to pick up Lenalidomide 10 mg 21 caps from R2GDPGOTEL (9 capsules used) and Lenalidomide 10 mg 21 Caps from GEM-CLARIDEX was delivered, indicating that he should complete the 12 days of the cycle.

Cabueñes Hospital	5	17.05.2017	Patient 348-1: Cycle 1 did not have serum free light chains analyzed in the response assessment section. Patient 348-2: In cycles 1, 3 and 8 serum free light chains were not analyzed in the response evaluation section. Patient 348-5: Ejection fraction was not measured in the baseline scan section during screening.
Cabueñes Hospital	6	13.08.2019	Patient 348-25: Cycle 8 - Response evaluation: serum free light chains are not determined. Patient 348-32: Screening - Baseline blood test: ß2-microglobulin value is not determined. Patient 348-31: Cycle 1 - Response assessment: no determination of CM in urine. Cycle 1 - Patient does not complete the Quality of Life Questionnaire. Final Visit - Response evaluation: no urine CM determined. Patient 348-33: Cycle 1 - Response assessment: no urine CM determined. Cycle 2 - Patient Status: ECOG not determined. Cycle 3 - Response evaluation: serum free light chains are not determined.
Cabueñes Hospital	7	14.02.2020	Patient 348-2: Cycle 1: Patient Status: hematologic values are not determined on days 8, 15 and 22 of the first cycle. Cycles 3, 4 and 5: Patient Status: ECOG not determined. Cycle 5: Response evaluation: urine CM value is not obtained. Patient 348-3 Cycles 44, 45 and 46: Patient Status: ECOG not determined. Cycles 42 and 44: Response evaluation: urine MC value is not obtained. Patient 348-5 Cycles 33, 34, 36, 39 and 40: Response evaluation: no urine MC value obtained. Cycle 37: Response evaluation: no serum MC value obtained. Patient 348-7 Cycle 9: Response evaluation: urine MC not determined. Patient 348-9 Cycles 9, 10 and 30: Response evaluation: no urine MC determined. Cycle 31: Response evaluation: urine MC and free light chains are not determined.

Cabueñes Hospital	8	14.02.2020	Patient 348-10 Cycles 29, 33 and 34: Response evaluation: no urine MC value obtained. Cycle 30: Response evaluation: no free light chain values are obtained. Cycle 31: Response evaluation: urine MC and free light chains are not determined. Cycles 30 and 32: Quality of life: quality of life questionnaires are not completed. Patient 348-13 Cycle 30: Response evaluation: urine MC value is not obtained. Patient 348-23 Cycle 8: Response evaluation: urine MC value is not determined. Cycle 21: Response evaluation: urine MC and free light chains are not determined. Patient 348-28 Cycles 19 and 20: Response evaluation: urine MC value is not obtained. Cycle 20: Quality of life: quality of life questionnaire is not completed. Patient 348-32 Cycle 9: Response evaluation: urine MC value not obtained. Patient 348-34 Cycles 2, 3, 4 and 6: Patient Status: ECOG not determined. Cycles 3, 6, 7 and 8: Response evaluation: no urine CM value obtained. Cycle 9: Response evaluation: free light chain value is not determined.
Cabueñes Hospital	9	15.10.2020	Patient 348-3: Cycle 52: Response evaluation: CM in serum and CM in urine. Cycle 53: Response evaluation: CM in urine.. Patient 348-5: Cycles 44 and 49: Patient Status: ECOG. Patient 348-10: Cycles 39 and 40: Patient status: ECOG. Cycle 12: Response evaluation: serum CM and serum free light chains. Cycles 41 and 43: Response evaluation: CM in urine. Patient 348-16: Final visit: ECOG.
Cabueñes Hospital	10	14.03.2021	The following protocol-mandated tests were not performed: Patient 348-3: - Cycle 58: Patient Status: ECOG. - Cycle 59: Patient Status: ECOG.

Cabueñes Hospital	11	14.03.2021	The following protocol-mandated tests were not performed: Patient 348-5: Cycles 49: Response evaluation: urine CM.
Cabueñes Hospital	12	14.03.2021	The following protocol-mandated tests were not performed: Patient 348-9: Cycles 41, 43 and 45: Response evaluation: urine CM.
Cabueñes Hospital	13	14.03.2021	The following tests stipulated by protocol were not performed: Patient 348-13: Cycle 41: Response evaluation: serum free chains.
Cabueñes Hospital	14	14.03.2021	The following protocol-mandated tests were not performed: Patient 348-34: Cycle 19: Patient Status: ECOG.
Cabueñes Hospital	15	14.03.2021	The following tests stipulated by protocol were not performed: Patient 348-03: Cycles 25-30: Quality of Life Form.
Cabueñes Hospital	16	14.03.2021	The following protocol-mandated tests were not performed: Patient 348-10: Cycle 38: Quality of Life Form
Cabueñes Hospital	17	14.03.2021	The following tests stipulated by protocol were not performed: Patient 348-05: - Cycles 25, 26, 35: Quality of Life Form. - Cycles 26, 27 and 28: Patient Status: ECOG
Cabueñes Hospital	18	16.09.2021	The following tests stipulated by protocol were not performed: Patient 348-03: - Cycles 25-30: Quality of Life Form. - Cycles 44-46, 58, 59: Patient Status: ECOG
Cabueñes Hospital	19	16.09.2021	The following tests stipulated by protocol were not performed: Patient 348-05: - Cycles 26, 27, and 28: Patient's Status: ECOG - Cycles 25, 26 and 35: Quality of Life Form - Cycle 37, 48: Response Evaluation: Urine CM
Cabueñes Hospital	20	16.09.2021	The following protocol-mandated tests were not performed: Patient 348-10: Cycle 38: Quality of Life Form

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
León Hospital	1	04.09.2017	Patient 349-01 The following protocol deviations were detected: - Cycle 4 and cycle 5 - Response evaluation: free light chains (sFLC-κ and sFLC-λ) are not determined. - Cycle 12 - Response evaluation: Serum CM is not determined. - Cycle 14 - Response evaluation: No determination of CM in urine.
León Hospital	2	04.09.2017	Patient 349-05 The following protocol deviations were detected: Selection - Baseline scan: Ejection Fraction is not determined. - Plasmacytomas: Transverse and axial sizes are not determined for the different locations indicated.
León Hospital	3	26.11.2018	Patient 349-01 The following protocol deviations were detected: Cycle 1 - Response evaluation: urine immunofixation is not performed. Cycles 2, 7, 11, 16, 19 and 21 - Response evaluation: No determination of CM in urine. Cycle 23 - Response evaluation: No serum MC or urine MC determined. Cycle 25 - Response evaluation: No determination of MC in urine.
León Hospital	4	26.11.2018	Patient 349-5 The following protocol deviations were detected: Cycle 3 - Response evaluation: No determination of MC in urine.
León Hospital	5	26.11.2018	Patient 349-16 The following protocol deviations were detected: Cycle 2 - Quality of Life: Patient does not complete the FACIT questionnaire.
León Hospital	6	12.11.2019	Patient 349-1: The following protocol specified tests were not performed: Cycles 1, 2, 3, 4, 13, 28, 30, 32 and 33 - response assessment: Immunofixation in urine. Cycles 28, 29 and 33 - response assessment: free light chains in serum.
León Hospital	7	12.11.2019	Patient 349-3 The following protocol specified tests were not performed: Cycles 16, 18, 19, 20 and 22 - response assessment: Immunofixation in urine. Cycles 3, 13, 14 and 21 - response assessment: CM urine. Cycles 14 and 20 - response assessment: free light chains in serum.
León Hospital	8	12.11.2019	Patient 349-4 The following protocol specified tests were not performed: Cycles 1, 3, 4, 8, 10, 10, 11, 12, 14, 15 and 16 - response evaluation: Immunofixation in urine.
León Hospital	9	12.11.2019	Patient 349-8 The following protocol specified tests were not performed: Cycles 1, 2, 3, 14 and 18 - response evaluation: Immunofixation in serum Cycle 18 - response evaluation: Immunofixation in urine

León Hospital	10	12.11.2019	Patient 349-15 The following protocol specified tests were not performed: Cycle 3 - response assessment: CM urine.
León Hospital	11	12.11.2019	Patient 349-16 The following protocol specified tests were not performed: Cycle 2 - response assessment: CM urine.
León Hospital	12	12.11.2019	Patient 349-17 The following protocol specified tests were not performed: Cycle 6 - response assessment: CM urine.
León Hospital	13	12.11.2019	Patient 349-18 The following protocol specified tests were not performed: Cycles 10, 13, 16, 17 and 18 - response evaluation: serum immunofixation. Cycle 1, 13, 14, 16, 18 and 19 - response evaluation: Immunofixation in urine. Cycles 10 and 17 - response evaluation: CM urine. Cycles 13 and 18 - response evaluation: serum free light chains.
León Hospital	14	12.11.2019	Patient 349-21 The following tests specified by protocol were not performed: Screening - baseline examination: ejection fraction not determined. Final visit - response assessment: CM urine. Cycle 1 - response assessment: urine MC.
León Hospital	15	12.11.2019	Patient 349-22 The following tests specified by protocol were not performed: Death - death: exact date of day of exitus not recorded. Cycle 4 - response evaluation: CM urine.
León Hospital	16	12.11.2019	Patient 349-23 The following protocol specified tests were not performed: Screening - baseline examination: no determination of ejection fraction. Cycle 1 - response assessment: urine CM.
León Hospital	17	12.11.2019	Patient 349-27 The following protocol specified tests were not performed: Cycle 3 - response assessment: Immunofixation in urine.
León Hospital	18	12.11.2019	Patient 349-28 The following protocol specified tests were not performed: Cycle 1 - response assessment: serum free light chains.
León Hospital	19	06.02.2020	Patient 349-1: The following protocol specified tests were not performed: Cycles 31, 36 and 37 - response assessment: urine CM. Cycles 10, 15, 34, 35, 38, 39, 40 and 41 - response evaluation: Immunofixation in urine. Cycles 34, 35 and 36 - response evaluation: serum free light chains.

León Hospital	20	06.02.2020	Patient 349-3: The following protocol specified tests were not performed: Cycles 25 and 29 - response assessment: urine CM. Cycles 17, 28, 30, 31 and 32 - response evaluation: Immunofixation in urine.
León Hospital	21	06.02.2020	Patient 349-4: The following protocol specified tests were not performed: Cycles 2, 5 and 7 - response assessment: urine CM. Cycles 6, 17, 18 and 19 - response evaluation: Immunofixation in urine.
León Hospital	22	06.02.2020	Patient 349-5: No se realizaron las siguientes pruebas especificadas por protocolo: Ciclos 3, 4 and 5- evaluación de la respuesta: CM orina.
León Hospital	23	06.02.2020	Patient 349-10: The following protocol specified tests were not performed: Screening - baseline screening: ejection fraction. Cycle 8 - response assessment: serum immunofixation.
León Hospital	24	06.02.2020	Patient 349-14: The following protocol-specified tests were not performed: Screening - baseline examination: ejection fraction. Final visit - response evaluation: not evaluated due to Patient exitus. Cycle 1 - response evaluation: serum immunofixation.
León Hospital	25	06.02.2020	Patient 349-15: The following tests specified by protocol were not performed: Final Visit - response assessment: urine CM. Cycle 2 - response evaluation: Immunofixation in urine.
León Hospital	26	06.02.2020	Patient 349-17: The following tests specified by protocol were not performed: Cycle 8 - response evaluation: Lacks analytics to perform response evaluation so far.
León Hospital	27	06.02.2020	Patient 349-18: The following protocol specified tests were not performed: Cycle 26 - response evaluation: serum immunofixation. Cycle 24 and 26 - response evaluation: Urine immunofixation. Cycles 2 and 25 - response evaluation: CM urine.
León Hospital	28	06.02.2020	Patient 349-23: The following protocol specified tests were not performed: Cycle 11 - response evaluation: urine CM. Cycle 13 - response evaluation: not evaluated due to Patient exitus.

León Hospital	29	19.08.2020	Patient 349-1: The following tests specified by protocol were not performed: Screening: Baseline scan: ejection fraction. Cycles 14, 26, 30, 33, 36 and 38: Patient Status: ECOG. Cycles 45, 46 and 47: Patient Status: vital signs. Cycle 42: Response evaluation: CM in urine. Cycles 43, 44 and 46: Response Evaluation: Urine Immunofixation. Cycle 45 and 47: Response evaluation: Immunofixation in urine and serum free light chains. Cycle 45: Quality of life: the form is not performed.
León Hospital	30	19.08.2020	Patient 349-3: The following tests specified by protocol were not performed: Screening: Baseline screening: ejection fraction. Cycles 33 and 34: Response evaluation: Immunofixation in urine. Cycle 35: Response evaluation: Serum CM, urine CM and serum free light chains. Cycles 36, 37 and 38: Response evaluation: CM in urine and serum free light chains. Cycles 36, 37 and 38: Quality of life: form not completed.
León Hospital	31	19.08.2020	Patient 349-8: The following tests specified by protocol were not performed: Cycles 5, 8, 10, 15 and 35: Response evaluation: serum immunofixation. Cycle 13: Response evaluation: CM in urine and Immunofixation in serum. Cycle 22: Response evaluation: serum free light chains. Cycles 24, 25 and 27: Response evaluation: Immunofixation in serum and urine. Cycles 26 and 34: Response evaluation: CM in urine. Cycle 28: Response evaluation: CM in urine, Immunofixation in serum and free light chains in serum. Cycles 31 and 36: Response evaluation: Immunofixation in serum and urine and serum free light chains. Cycle 33: Response evaluation: Immunofixation in urine.
León Hospital	32	19.08.2020	Patient 349-18: The following protocol specified tests were not performed: Cycles 28 and 30: Response evaluation: Immunofixation in serum and urine. Cycle 29: Response evaluation: Immunofixation in serum. Cycle 31: Response evaluation: CM in serum and Immunofixation in urine.
León Hospital	33	19.08.2020	Patient 349-25: The following protocol specified tests were not performed: Cycle 9: Response evaluation: CM in urine and free light chains in serum. Cycles 11, 12 and 16: Response evaluation: CM in urine. Cycle 15: Response evaluation: Immunofixation in urine and serum free light chains.
León Hospital	34	19.08.2020	Patient 349-27: The following protocol-specified tests were not performed: Screening: baseline CBC: β2 Microglobulin. Cycles 4 - 10, 17 and 18: Response evaluation: Immunofixation in urine. Cycle 11: Response evaluation: CM in urine and free light chains in serum. Cycle 13: Response evaluation: CM in urine. Cycles 14 - 16: Response evaluation: Immunofixation in urine and serum free light chains.

León Hospital	35	19.08.2020	Patient 349-28: The following protocol-specified tests were not performed: Cycle 11: Patient Status: ECOG. Cycles 16 - 18: Patient Status: vital signs. Cycles 3, 5 - 9, 17: Response Evaluation: Urine Immunofixation. Cycles 4, 10: Response evaluation: Immunofixation in urine and serum free light chains. Cycles 11 - 13, 15 and 18: Response evaluation: Immunofixation in serum and urine. Cycle 14: Response evaluation: CM in urine. Cycle 16: Response evaluation: CM in urine and Immunofixation in serum.
León Hospital	36	03.12.2020	Patient 349-3: The following protocol-specified tests were not performed: - Patient status: - Cycle 1: hematologic values on day 22 of treatment. - Cycles 14, 15, 17, 22 and 25: ECOG. - Cycles 36, 37 and 40-42: vital signs. - Response evaluation: - Cycles 39-41: serum CM (gr/dL), urine CM (gr/24H) and serum free light chains. - Quality of life: - Cycles 8, 11 and 38.
León Hospital	37	03.12.2020	Patient 349-8: The following tests specified by protocol were not performed: - Screening: - Baseline scan: ejection fraction (%). - Relevant medical history: year of diagnosis. - Bone assessment: bone series result. - PET-CT. - Patient's status: - Cycle 3: ECOG. - Quality of life: - Cycles 33 and 34
León Hospital	38	03.12.2020	Patient 349-10: The following protocol-specified tests were not performed: - Quality of life: - Cycles 6 and 8.

León Hospital	39	18.05.2021	Patient 349-1: The following protocol-specified tests were not performed: - Patient status: - Cycles 49 and 52: vital signs - Cycle 50: ECOG - Cycle 51: ECOG and vital signs - Response evaluation: - Cycle 48: urine IF and serum free light chains - Cycles 49-53: IF in urine - Cycles 54 and 55: serum free light chains. - Quality of life: - Cycle 55
León Hospital	40	18.05.2021	Patient 349-3: The following protocol-specified tests were not performed: - Patient Status: - Cycles 43 and 44: ECOG and vital signs. - Cycle 46: biochemical values - Response evaluation: - Cycle 42: serum CM and urine CM - Cycles 43-45: CM serum, CM urine and serum free light chains - Quality of life: - Cycles 42 and 43
León Hospital	41	18.05.2021	Patient 349-8: The following protocol-specified tests were not performed: - Patient status: - Cycle 34: Vital Signs. - Response Evaluation: - Cycles 37-39 and 41: IF in urine - Quality of Life: - Cycles 38, 39 and 41-43
León Hospital	42	18.05.2021	Patient 349-27: The following protocol-specified tests were not performed: - Response evaluation: - Cycles 19-21 and 23: IF in urine - Cycle 22: urine IF and serum free light chains - Cycle 25: CM urine and serum free light chains
León Hospital	43	18.05.2021	Patient 349-28: The following tests specified by protocol were not performed: - Final visit: vital signs - Response assessment: - Cycle 25: serum free light chains. - Quality of life: - Cycle 25

León Hospital	44	17.11.2021	Patient 349-3: The following protocol-specified tests were not performed: - Response evaluation: - Cycles 46, 47, 48, 50: serum CM, urine CM and serum free light chains.
León Hospital	45	17.11.2021	Patient 349-8: The following protocol-specified tests were not performed: - Response evaluation: - Cycle 46: serum free light chains. - Quality of life: - Cycle 46
León Hospital	46	17.11.2021	Patient 349-18: The following protocol-specified tests were not performed: - Response evaluation: - Cycles 39, 42: IF in urine. - Cycle 43: CM in urine and serum free light chains
León Hospital	47	17.11.2021	Patient 349-27: The following protocol-specified tests were not performed: - Response evaluation: - Cycles 24, 30, 31: IF in urine and serum free light chains. - Cycles 26-29: urine IF
León Hospital	48	17.11.2021	Patient 349-28: The following protocol-specified tests were not performed: - Response evaluation: - Cycle 19: IF in serum, IF in urine and free light chains in serum. - Cycle 20, 22: Serum IF and urine IF - Cycle 23: CM in urine, IF in urine and IF in serum
León Hospital	49	06.09.2022	Patient 349-1 The following protocol-specified tests were not performed: Response Evaluation. - Cycles 56, 58, 60, 63, 66 light chains - Cycles 57-60, 62, 63-67 immunofixation urine - Cycle 61 cm urine Patient Status - Cycles: 57, 58, 59, 60, 60, 61, 62, 63-70 Vital Signs - Cycles: 63, 67 ECOG Quality of Life - Cycles 64, 67

León Hospital	50	20.10.2022	Patient 349-3 The following tests specified by protocol were not performed: - Plasmacytoma selection: size other lesions. - Patient Status: cycles 47,51, 52 vital signs - Patient Status: Cycles 47,47, 52 biochemical values - Response evaluation: cycles 49, 51, 52 complete analysis - Quality of life: cycles 51, 52
León Hospital	51	20.10.2022	Patient 349-8 The following tests specified by protocol were not performed: - Final V.: vital signs and ECOG. - Patient Status: cycles 2, 18 ECOG - Patient Status: cycles 5, 44, 53 vital signs - Response Evaluation: Cycles 52 CM urine - Quality of life: cycles 51, 52, 53
León Hospital	52	20.10.2022	Patient 349-18 The following protocol-specified tests were not performed: - Screening: Bone assessment
León Hospital	53	16.05.2023	Patient 349-01 The following protocol specified tests were not performed: Cycle 71: In the Response Evaluation, free chains were not measured. Cycle 74,75,76: ECOG is not performed.
León Hospital	54	16.05.2023	Patient 349-18 The following tests specified by protocol were not performed: Cycle 30: Quality of life questionnaire not performed. Cycle 37,38,40,48 : ECOG not performed.
León Hospital	55	16.05.2023	Patient 349-01 The following tests specified by protocol were not performed: Cycle 38: The Patient quality questionnaire is not performed.
León Hospital	56	16.05.2023	Patient 349-18 The following protocol-specified tests were not performed: Cycle 15, 26,33,45 : Quality of life questionnaire not performed.
León Hospital	57	16.05.2023	Patient 349-27 The following protocol specified tests were not performed: Cycle 3,5,8,12,13,17 : ECOG was not performed.

León Hospital	58	30.08.2023	<u>Patient 349-18</u>
			The following tests specified by protocol were not performed:
			- Final visit:
			  - Plasmacytomas.
			- Patient Status:
			  - Cycle 8, 16 and 64: ECOG was not performed.
			- Response Evaluation:
			  - Cycles 53 and 56: Free light chains in serum.
			  - Cycle 56: Immunofixation in serum.
			  - Cycle 62: Immunofixation in serum.

León Hospital	59	30.08.2023	<u>Patient 349-27</u> The following protocol specified tests were not performed: Cycle 37, 40, 43 and 45: Response evaluation: Serum light chains.
León Hospital	60	30.08.2023	<u>Patient 349-01</u> The following tests specified by protocol were not performed: - Final Visit: ECOG not performed. - Response evaluation: - Cycle 76 and 77: Urine immunofixation is not performed.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
La Fe Hospital	1	29.09.2017	Patient 358-3 - Selection - Disease at diagnosis: Free light chains are not determined - Baseline examination: Ejection fraction is not determined.
La Fe Hospital	2	29.09.2017	Patient 358-3 - Selection - Disease at diagnosis: Free light chains are not determined - Baseline examination: Ejection fraction is not determined.
La Fe Hospital	3	27.07.2018	Patient 358-2 - Selection - Disease at diagnosis: CMo value is not determined. - Baseline scan: Ejection Fraction is not determined. - Cycle 1: Response evaluation: CMo value is not determined.
La Fe Hospital	4	27.07.2018	Patient 358-3 - Cycle 1: Patient Status: Vital signs are not determined. - Cycle 2: Response Evaluation: CMo value is not determined. - Cycle 3: Response Evaluation: CMo value is not determined. - Cycle 9: Response Evaluation: Serum free light chains are not determined.
La Fe Hospital	5	04.02.2019	Patient 358-4 - Screening - Disease at diagnosis: CMo value is not determined. - Screening - Baseline examination: Weight, height and Ejection Fraction are not determined. - Cycle 1 - Response evaluation: Serum free light chains are not determined. - Cycle 1 - Quality of Life: Quality of Life Questionnaire, FACIT, is not performed. - V. Final - Response evaluation: Serum free light chains are not determined.
La Fe Hospital	6	04.02.2019	Patient 358-5 - Selection - Baseline Scan: Ejection Fraction is not determined. - Cycle 1: Patient Status: CMs and CMo values are not determined. - V. Final: Patient Status: CMs and CMo values are not determined.
La Fe Hospital	7	05.08.2019	Patient 358-6 - Selection - Height is not determined. - Cycle 7 - Response Evaluation: Serum free light chains are not determined. - Cycles 9-11, 13 and 14 - Patient Status: ECOG is not determined.
La Fe Hospital	8	05.08.2019	Patient 358-7 - Cycle 1 - Response evaluation: CMo is not determined. - Cycle 4 - Response evaluation: Neither CMo nor serum free light chains are determined. - Cycle 8 - Response evaluation: No determination of CMo.
La Fe Hospital	9	17.02.2020	Patient 358-3 - Cycles 2, 3, 4, 5 and 6: Quality of life: no quality of life questionnaire - Cycle 9: Response evaluation: no serum free light chains are determined.
La Fe Hospital	10	17.02.2020	Patient 358-5 Cycle 1: Patient's status: ECOG is not determined.

La Fe Hospital	11	17.02.2020	Patient 358-6 Cycles 17, 18, 19 and 20: Patient's status: ECOG not determined.
La Fe Hospital	12	17.02.2020	Patient 358-7 - Final visit: Response evaluation: no determination of MC in urine - Cycle 12: Response evaluation: no determination of MC in urine.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Dr. Peset Hospital	1	02.11.2016	Patient 357-1: - Selection: - In the "Relevant medical history" section of the e-CRD, it is reflected that the Patient suffers from hypertension and cataracts but the date of diagnosis of these pathologies is unknown. -In the "PET CT" section of the e-CRD, the presence of a pathological PET CT scan is reflected but its distribution is unknown. - It is verified that the data reflected in the "Bone marrow aspirate" section of the e-CRD come from the local laboratory. According to the protocol, a bone marrow sample should be sent to the reference laboratory during the screening process. The monitor informs of the importance of sending such a sample, even if a recent bone marrow aspirate has been performed, as it is an essential test to compare the cellular evolution of the Patient pre and post treatment.
Dr. Peset Hospital	2	02.11.2016	Patient 357-2: During the monitoring visit dated November 2, 2016, Dr. de la Rubia asks the monitor for consultation on the inclusion of a Patient who despite having been treated with a single dose of Velcade, is a candidate for entry into the study as indicated by the tests performed so far. Dr. De la Rubia advises to enter the GEM CLARIDEX study as the best therapeutic option for his disease. The monitor transfers this issue to the coordinators of the study who, on November 4, give their approval to include this Patient. On November 7, 2016, Patient 357-2 signs the IC and begins the screening tests.
Dr. Peset Hospital	3	07.05.2018	Patient 357-9: On day +15 of cycle 2, Dr. Cejalvo reviews the treatment intake with the Patient and verifies that, by mistake, he has taken the following medication: - 5 tablets of Lenalidomide 25mg (total dose 125 mg) on December 14 and 21. - 1 tablet of Fortecortin 5mg once a day since December 14. Subsequently, she checks that the documentation given to the Patient shows that the prescription is correct. Dr. Cejalvo verifies that the Patient is asymptomatic, shows no clinical deterioration, no type of toxicity attributable to taking Lenalidomide and in the hemogram does not show any cytopenia. According to the instructions of the AEMPS "serious non-compliance shall be understood as that which can significantly compromise the safety and rights of the trial subjects". Therefore, the monitor transfers this issue to the study coordinators who, on January 2, 2018, indicate to Dr. Cejalvo to suspend Lenalidomide treatment until the end of cycle 2 and resume the dose of Dexamethasome that corresponds to her on day 21 of cycle 2. She is also asked to consider training the patient prior to starting cycle 3.
Dr. Peset Hospital	4	30.09.2019	Patient 357-2: - Cycle 1: no immunofixation in urine and no determination of free light chains in serum - Cycle 2: no determination of MC in urine.

Dr. Peset Hospital	5	05.02.2020	The following tests stipulated by protocol were not performed: Patient 357-13: - Screening: Baseline CBC: β2 Microglobulin. - Selection: Disease at Diagnosis: ECOG - Selection: Baseline Exam: Weight and height. - Cycle 1: Quality of life: no questionnaire. - Cycles 1 and 6: Patient Status: ECOG - Cycle 2: Response evaluation: CM in urine. - Cycle 5: Response evaluation: CM in serum, CM in urine, Oligloclonal Bands, and Free Light Chains in serum. - Cycle 6: Response evaluation: serum free light chains. - Cycle 7: Response evaluation: CM in urine and immunofixation in serum.
Dr. Peset Hospital	6	05.02.2020	The following tests stipulated by protocol were not performed: Patient 357-15: - Cycles 5, 6, 7 and 10: Response evaluation: serum free light chains. - Cycles 9 and 13: Response evaluation: CM in urine. - Cycle 12: Response evaluation: Immunofixation in urine and serum free light chains.
Dr. Peset Hospital	7	05.02.2020	The following protocol-mandated tests were not performed: Patient 357-16: - Cycle 1: Response Evaluation: CM in urine and Free Light Chains in serum. - Cycle 2: Patient Status: ECOG - Cycle 2: Response evaluation: urine CM - Cycles 3, 4 and 5: Response Evaluation: Serum Free Light Chains. - Cycles 7 and 11: Response evaluation: immunofixation in urine.
Dr. Peset Hospital	8	26.01.2023	The following tests stipulated by protocol were not performed: Patient 357-10: -Cycle 39: quality of life questionnaire. -Cycles 41, 42, 43, 44, 45, 46, 47, 48 and 50: response evaluation: urine immunofixation.
Dr. Peset Hospital	9	12.08.2021	Patient 357-16: - Cycles 3 and 7: the quality of life questionnaire is not carried out.
Dr. Peset Hospital	10	26.01.2023	The following tests stipulated by protocol were not performed: Patient 357-15: -Cycle 39: quality of life questionnaire. -Cycles 41, 42, 43, 44, 45, 46, 47, 48 and 50: response evaluation: urine immunofixation.
Dr. Peset Hospital	11	26.01.2023	The following protocol-mandated tests were not performed: Patient 357-10: -Cycle 39: quality of life questionnaire. -Cycles 41, 42, 43, 44, 45, 46, 47, 48 and 50: response evaluation: urine immunofixation.
Dr. Peset Hospital	12	25.05.2023	Patient 357-2: Cycle 3, 8: No measurement of serum free chains or serum MC is performed in the response evaluation.
Dr. Peset Hospital	13	25.05.2023	Patient 357-3: - Screening: Bone assessment is not performed. - Final visit: Plasmacytomas are not measured. Response assessment was not performed at this visit due to Patient's death. - Cycle 5: Quality of life questionnaire is not performed.

Dr. Peset Hospital	14	25.05.2023	Patient 357-6: - Final visit: No urine CM was performed. - Cycle 3: ECOG is not performed. - Cycle 22: No CM in urine. - Cycle 24: No serum free chains were measured.
Dr. Peset Hospital	15	25.05.2023	Patient 357-8: - Selection: In diagnostic disease neither ECOG is performed nor CM is measured in urine. In addition, bone assessment was not performed and plasmacytomas were not measured. - Final visit: No response evaluation or plasmacytoma measurement was performed due to the death of the patient.
Dr. Peset Hospital	16	25.05.2023	Patient 357-9: - Final visit: In the evaluation of the response, the measurement of free chains is not performed. - Cycle 5: Quality of life is not performed in this cycle.
Dr. Peset Hospital	17	25.05.2023	Patient 357-10: - Cycle 9,35: Free chains are not measured in the response evaluation. - Cycle 35: Response evaluation is not performed. - Cycle 6: The quality of life questionnaire is not performed in this cycle.
Dr. Peset Hospital	18	25.05.2023	Patient 357-12: - Selection: In the baseline scan LVEF is not measured and PET-CT is not performed. - Cycle 1,2,3,4,5,6 and 7: ECOG is not performed. - Cycle 15: Response evaluation is not performed in this cycle.
Dr. Peset Hospital	19	25.05.2023	Patient 357-15: The following tests stipulated by protocol are not performed: - Cycle 2,3,5,53, 55: Quality of life questionnaire is not performed. - Cycle 16: Response assessment is not performed in this cycle because Patient had COVID-19. - Cycle 17,53,55: ECOG is not performed. - Cycle 52, 54: Response evaluation not performed. - Cycle 53,55: In response evaluation, CM is not measured in urine. - Final visit: Response evaluation not performed.
Dr. Peset Hospital	20	25.05.2023	Patient 357-16: The following tests stipulated by protocol are not performed: - Final visit: ECOG is not performed.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Morales Messenguer Hospital	1	10.11.2016	Patient 351-01 The following protocol deviations were detected: - Selection: - In the section "Relevant medical history" of the e-CRD, it is reflected that the Patient suffers from hypertension, dyslipidemia, knee prosthesis and vertiginous syndrome, however, the date of diagnosis of these pathologies is unknown, the Study Coordinator comments to the monitor that this information was not in the clinical history available to them, in addition the Patient would have discontinued the one that would make it difficult to obtain this information. - Cycle 1: - In the "Response Evaluation" section of the e-CRD, the urine MC value (gr/24H) is not reflected. The Study Coordinator reports that the source test shows a positive urine IF but the proteinuria could not be calculated as the 24h urine volume was not known. - Cycle 2 and final visit: - In the "Response evaluation" section of the e-CRD, neither the urine MC value nor the light chains are reflected. The Study Coordinator comments to the monitor that when the Patient left the study, the urine immunofixation, proinogram and light chains were not requested from the laboratory.
Morales Messenguer Hospital	2	22.06.2017	Patient 351-09 The following test stipulated by protocol was not performed: Screening - Baseline scan: Ejection Fraction is not determined.
Morales Messenguer Hospital	3	22.06.2017	Patient 351-06 The following tests stipulated by protocol were not performed: Screening - Disease at diagnosis: Free light chains (sFLC-κ and sFLC-λ) are not determined. - Baseline examination: Weight, height and Ejection Fraction are not determined. Cycle 1 - Patient Status: ECOG is not determined.
Morales Messenguer Hospital	4	22.06.2017	Patient 351-07 The following tests stipulated by protocol were not carried out: Screening - Disease at diagnosis: No determination of urine CM and free light chains (sFLC-κ and sFLC-λ). - Baseline screening: Ejection Fraction not determined.
Morales Messenguer Hospital	5	22.06.2017	Patient 351-08 The following test stipulated by protocol was not performed: Screening - Baseline scan: Ejection Fraction is not determined.
Morales Messenguer Hospital	6	21.03.2018	Patient 351-15 Patient is having excessive toxicity to treatment (currently on D35C2), so the start of cycle 3 is being delayed due to poor general condition. Cycle 2 was started with a reduction of one dose level and, per protocol, the third cycle should be started with a reduction of an additional dose level: 15 mg/day. Dr. de Arriba requests authorisation to start cycle 3 with a reduction of two dose levels (10 mg/day), as this will allow better tolerance to the treatment and thus continue in the study. The monitor transfers this consultation to the study coordinators who, on 22 March 2018, accept this reduction of two dose levels.

Morales Messenguer Hospital	7	02.10.2018	Patient 351-02 The following tests stipulated by protocol were not performed: Screening - Baseline Scan: Ejection Fraction is not determined. Cycle 2 - Patient Status: ECOG not determined. - Response Evaluation: CMo is not determined. Cycle 3 - Patient Status: ECOG is not determined. Cycle 4 - Patient Status: ECOG not determined. - Response Evaluation: No serum free light chains determined. Cycle 5 - Patient Status: ECOG not determined.
Morales Messenguer Hospital	8	02.10.2018	Patient 351-03 The following tests stipulated by protocol were not performed: Screening - Baseline CBC: No determination of corrected calcium and ß2-microglobulin. - Baseline examination: Ejection fraction is not determined. - Relevant Medical History: The year of diagnosis of vertigo is not indicated. Cycle 1 - Response Assessment: No serum or urine immunofixation performed. - Quality of life: Quality of life questionnaire not performed. Cycle 1 - Quality of life: Quality of life questionnaire not performed. Final Visit - Final Visit: ECOG not determined.
Morales Messenguer Hospital	9	02.10.2018	Patient 351-05 The following tests stipulated by protocol were not performed: Screening - Baseline scan: no weight or Ejection Fraction determined. Cycles 1, 2 and 4 - Response evaluation: CMo is not determined. Cycle 6 - Response evaluation: Serum immunofixation is not performed.
Morales Messenguer Hospital	10	07.03.2019	Patient 351-03 The following tests stipulated by protocol were not performed: Screening - Disease at diagnosis: CMo is not determined.
Morales Messenguer Hospital	11	07.03.2019	Patient 351-10 The following protocol-mandated tests were not performed: Cycle 1 - Response Evaluation: CMo is not determined. Cycle 2 - Response evaluation: Urine Immunofixation is not determined. Cycle 3 - Response Evaluation: No determination of CMo. Cycle 5 - Patient Status: ECOG is not determined. Cycle 6 - Response Evaluation: Serum Free Light Chains are not determined. Cycle 8 - Response Evaluation: No determination of Immunofixation in urine. Cycle 11 - Response evaluation: CMo is not determined.
Morales Messenguer Hospital	12	07.03.2019	Patient 351-13 The following tests stipulated by protocol were not performed: Screening - Disease at diagnosis: ECOG is not determined. Screening - Disease at diagnosis: Height, weight and ejection fraction are not determined. Cycle 1 - Patient Status: ECOG is not determined. Cycles 3-5 - Response Evaluation: CMo is not determined. Cycles 6 and 7 - Patient Status: No ECOG determined. Cycle 8 - Response Evaluation: No CMo determined.

Morales Messenguer Hospital	13	07.03.2019	Patient 351-17 The following protocol-mandated tests were not performed: Screening - Disease at diagnosis: ECOG not determined.
Morales Messenguer Hospital	14	04.06.2019	Patient 351-02 The following tests stipulated by protocol were not performed: Cycles 6, 8, 14, 15 and 17 - Patient Status: ECOG not determined. Cycles 6, 7, 14, 15, 17, 19 and 21 - Response Evaluation: No determination of Immunofixation in serum and urine. Cycles 9 and 10 - Response evaluation: Immunofixation in urine is not determined. Cycle 13, 18, 20 and 22 - Response evaluation: Immunofixation in serum is not determined. Cycle 11 - Response evaluation: Serum CM and oligoclonal bands are not determined. Cycles 16 and 23 - Response evaluation: No determination of CM in urine or serum immunofixation.
Morales Messenguer Hospital	15	04.06.2019	Patient 351-06 The following tests stipulated by protocol were not performed: Cycle 2 - Response evaluation: serum Free Light Chains are not determined. Cycle 4, 8 - Response evaluation: CMo is not determined. Cycle 5, 9, 12 - Response evaluation: Immunofixation in urine is not determined. Cycle 3 - Patient Status: ECOG is not determined.
Morales Messenguer Hospital	16	04.06.2019	Patient 351-07 The following tests stipulated by protocol were not performed: Cycle 7, 11, 12, 12, 13, 14 - Patient Status: ECOG not determined. Cycle 2 - Response Evaluation: CMo is not determined. Cycle 3, 4 - Response Evaluation: Urine Immunofixation is not determined. Cycles 5, 9, 11, 12, 13, 14 and 17 - Response evaluation: Immunofixation in serum and urine is not determined. Cycle 6, 7, 8, 8, 10, 15 and 18 - Response evaluation: Immunofixation in serum is not determined. Cycle 16 - Response evaluation: Immunofixation in serum and urine and serum free light chains are not determined..
Morales Messenguer Hospital	17	14.01.2020	Patient 351-05 The following tests stipulated by protocol were not performed: Cycles 6, 12, 14, 16, 18, 20 and 21: Response evaluation: serum immunofixation is not determined. Cycles 8, 11: Response evaluation: urine CM and serum immunofixation are not determined. Cycle 9, 13, 15, 17: Response evaluation: serum immunofixation and urine immunofixation are not determined.
Morales Messenguer Hospital	18	14.01.2020	Patient 351-06 The following tests stipulated by protocol were not performed: Cycles 14, 16 and 19: Response evaluation: urine immunofixation is not determined. Cycles 6, 7 and 15: Quality of life: Quality of life questionnaire not performed. Protocol guidelines were not followed in the following cycles: Cycles 1-15: Medication: the patient, over 75 years of age, takes dexamethasome 40mg. The protocol indicates that for these Patients, the weekly dose is 20mg.
Morales Messenguer Hospital	19	14.01.2020	Patient 351-07 The following protocol-mandated tests were not performed: Cycle 26: Response evaluation: neither serum immunofixation nor urine immunofixation is determined. Cycle 27: Response evaluation: no determination of CM in urine or serum immunofixation. Cycles 28 and 29: Response evaluation: serum immunofixation is not determined.

Morales Messenguer Hospital	20	14.01.2020	Patient 351-09 The following protocol-mandated tests were not performed: Cycle 1: Response evaluation: no determination of CM in urine. Cycle 6: Response evaluation: no serum MC determined. Cycles 9 -22, 24, 26-29, 31 and 32: Response evaluation: no determination of immunofixation in urine. Cycle 23: Response evaluation: serum MC, urine immunofixation and oligoclonal bands are not determined. Cycles 5 and 7: Quality of life: Quality of life questionnaire is not performed.
Morales Messenguer Hospital	21	14.01.2020	Patient 351-10 The following tests stipulated by protocol were not performed: Cycles 7, 12, 14, 19, 21, 23, 25 and 27: Response evaluation: no urine immunofixation determined. Cycles 15 and 16: Response evaluation: urine CM is not determined. Cycles 20 and 22: Response evaluation: urine MC and serum free light chains are not determined.
Morales Messenguer Hospital	22	14.01.2020	Patient 351-12 The following protocol-mandated tests were not performed: Cycles 1 and 4: Response evaluation: no urine CM determined. Cycles 3 and 5: Response evaluation: no determination of urine immunofixation. Cycles 7, 9- 12, 14 and 15: Response evaluation: no serum immunofixation determined. Cycle 8, 13, 16, 17, 19, 21-23: Response evaluation: no serum immunofixation or urine immunofixation determined. Cycle 18: Response evaluation: no determination of CM in urine or serum immunofixation. Cycle 24: Response evaluation: neither serum MC nor urine immunofixation is determined.
Morales Messenguer Hospital	23	14.01.2020	From 04 June 2019 to 14 January 2020, the following temperature deviations have been found: - On the day 21/07/2019 a maximum temperature of 26.8 °C was recorded. - On the day 22/07/2019 a maximum temperature of 26.7 °C was recorded. - On 15/09/2019 a maximum temperature of 27.3 °C was recorded. - On 16/09/2019 a maximum temperature of 27.3 °C was recorded. - On 05/10/2019 a maximum temperature of 26.2 °C was recorded. - On 22/10/2019 a maximum temperature of 32.9 °C was recorded. - On 24/10/2019 a maximum temperature of 26.3 °C was recorded. - On 19/11/2019 a maximum temperature of 27.4 °C was recorded. - On 26/11/2019 a maximum temperature of 56.8 °C was recorded. - On 02/12/2019 a maximum temperature of 29.0 °C was recorded.
Morales Messenguer Hospital	24	22/07/2020 - 23/07/2020	Patient 346-08 The following tests stipulated by protocol were not performed: - Cycles 8, 16 and 18: Response evaluation: Immunofixation in urine. - Cycles 10 and 11: Response evaluation: urine CM. - Cycles 13, 14 and 23: Response evaluation: Serum immunofixation. - Cycle 15, 19-21 and 24-26: Response evaluation: Immunofixation in serum and urine. - Cycle 17: Response evaluation: Serum CM and urine immunofixation. - Cycles 22, 27 and 28: Response evaluation: CM in urine and Immunofixation in serum.

Morales Messenguer Hospital	25	22/07/2020 - 23/07/2020	Patient 351-04 The following tests stipulated by protocol were not performed: - Screening: Disease at Diagnosis: ECOG, CM in urine and free light chains in serum. - Screening: Baseline Scan: Weight and ejection fraction. - Cycle 1: Patient Status: ECOG. - Cycles 1 and 4: Response assessment: urine CM and serum free light chains. - Cycles 8, 9, 18, 19 and 30: Response evaluation: Immunofixation in urine. - Cycle 15: Response evaluation: CM in urine. - Cycle 21: Response evaluation: urine MC and urine immunofixation. - Cycles 28, 36 and 37: Response evaluation: Immunofixation in serum. - Cycles 29, 31-35 and 38-43: Response evaluation: Immunofixation in serum and urine.
Morales Messenguer Hospital	26	22/07/2020 - 23/07/2020	Patient 351-06 The following protocol-mandated tests were not performed: - Cycles 27, 28 and 34: Patient Status: ECOG. - Cycle 23: Response Evaluation: Immunofixation in serum and serum free light chains. - Cycles 24, 28, 31, 34: Response evaluation: Immunofixation in serum and urine. - Cycles 27, 29, 30: Evaluation of the response: Immunofixation in urine. - Cycle 32: Response evaluation: Immunofixation in serum. - Cycle 35: Evaluation of the response: Immunofixation in serum and urine and free light chains in serum. - Cycle 36: Response evaluation: CM in urine.
Morales Messenguer Hospital	27	22/07/2023 - 23/07/2020	Patient 351-07 The following tests stipulated by protocol were not performed: - Cycle 37: Patient Status: ECOG. - Cycles 23 and 37: Response evaluation: Serum immunofixation. - Cycles 22, 30-34 and 38: Response evaluation: Immunofixation in serum and urine. - Cycles 35 and 36: Response evaluation: CM in urine and serum immunofixation. - Cycles 6 and 17: Quality of life: form not completed.
Morales Messenguer Hospital	28	22/07/20520 - 23/07/2020	Patient 351-09 The following tests stipulated by protocol were not performed: - Cycles 33, 34, 36 and 37: Response evaluation: Immunofixation in urine.
Morales Messenguer Hospital	29	22/07/2020 - 23/07/2020	Patient 351-12 The following protocol-mandated tests were not performed: - Cycle 13: Patient Status: ECOG. - Cycle 25: Response evaluation: Immunofixation in serum - Cycles 26 and 29-31: Response evaluation: Immunofixation in serum and urine.
Morales Messenguer Hospital	30	22/07/2020 - 23/07/2020	Patient 351-13 The following tests stipulated by protocol were not performed: - Screening. Disease at diagnosis: ECOG. - Cycle 26: Patient status: ECOG. - Cycles 6, 10-12, 16, 18-22 and 24, 29: Response assessment: urine CM. - Cycles 13, 14, 23, 26-28, 30 and 31: Response evaluation: Immunofixation in urine. - Cycle 17: Response evaluation: CM in serum and urine, Oligoclonal Bands and Free Light Chains in serum. - Cycles 2, 4, 7, 8, 10 and 20: Quality of life: not completed.

Morales Messenguer Hospital	31	11/09/2020 - 12/09/2020	Patient 346-08 The following tests stipulated by protocol were not performed: - Cycles 14 and 33: Response evaluation: Immunofixation in serum. - Cycles 17 and 30: Response evaluation: Serum CM and urine immunofixation. - Cycles 31 and 32: Response evaluation: Immunofixation in serum and immunofixation in urine.
Morales Messenguer Hospital	32	11/09/2020 - 12/09/2020	Patient 351-02 The following tests stipulated by protocol were not performed: - Cycles 31, 32 and final visit: Response evaluation: serum immunofixation and urine immunofixation. - Cycles 28 and 30: Response evaluation: Serum immunofixation. - Cycle 29: Response evaluation: Immunofixation in urine. - Cycles 12 and 16: Quality of life: no questionnaire.
Morales Messenguer Hospital	33	11/09/2020 - 12/09/2020	Patient 351-04 The following tests stipulated by protocol were not performed: - Cycle 20: Response evaluation: Serum CM. - Cycles 26 and 48: Response evaluation: Immunofixation in serum.
Morales Messenguer Hospital	34	11/09/2020 - 12/09/2020	Patient 351-06 The following tests stipulated by protocol were not performed: - Cycle 28: Response evaluation: Serum immunofixation and urine immunofixation. - Cycles 37, 38 and 39: Response evaluation: CM in urine and Immunofixation in serum.
Morales Messenguer Hospital	35	11/09/2020 - 12/09/2020	Patient 351-08 The following protocol-mandated tests were not performed: - Cycle 2: Response evaluation: CM in urine and free light chains in serum. - Cycles 4 and 11: Response evaluation: CM in urine. - Cycles 5, 6 and 8: Response evaluation: Immunofixation in urine. - Cycle 13: Response evaluation: serum free light chains. - Cycle 11: Quality of life: no questionnaire. - Final visit: Response evaluation: Serum MC.
Morales Messenguer Hospital	36	11/09/2020 - 12/09/2020	Patient 351-09 The following tests stipulated by protocol were not performed: - Cycle 29: Patient Status: ECOG. - Cycles 41 and 42: Response evaluation: Urine Immunofixation.
Morales Messenguer Hospital	37	11/09/2020 - 12/09/2020	Patient 351-12 The following tests stipulated by protocol were not performed: - Screening: Baseline scan: ejection fraction. - Cycle 27: Response assessment: CM in serum and urine. - Cycles 32 and 34: Response evaluation: Immunofixation in serum and urine. - Cycle 33: Response evaluation: Immunofixation in serum. - Cycle 35: Quality of life: no questionnaire.
Morales Messenguer Hospital	38	11/09/2020 - 12/09/2020	Patient 351-13 The following tests stipulated by protocol were not performed: - Cycle 33: Response evaluation: Immunofixation in urine.

Morales Messenguer Hospital	39	11/09/2020 - 12/09/2020	Patient 351-14 The following protocol-mandated tests were not performed: - Cycles 1, 3, 4 and 7: Patient's status: ECOG - Cycle 2: Response evaluation: CM in serum and urine. - Cycles 4, 12 and 13: Response evaluation: CM in urine. - Cycles 8, 9 and 11: Response evaluation: Immunofixation in urine. - Cycles 5, 12 and 15: Quality of life: no questionnaire.
Morales Messenguer Hospital	40	15.04.2021	Patient 346-08 The following tests stipulated by protocol were not carried out: - Quality of life questionnaire: cycles 10, 14, 18, 26 and 30.
Morales Messenguer Hospital	41	15.04.2021	Patient 351-16: The following tests stipulated by protocol were not performed: - Cycle 1: Response evaluation: Immunofixation in serum. - Cycle 2: Response evaluation: Serum MC and detection of oligoclonal bands. - Cycle 3: Response evaluation: CM in urine and serum immunofixation. - Cycle 4: Response evaluation: Serum immunofixation. - Cycle 5: Response evaluation: Serum immunofixation. - Cycle 6: Response evaluation: Immunofixation in serum and urine. - Cycle 7: Response evaluation: Immunofixation in serum and urine. - Cycle 8: Response evaluation: Immunofixation in serum. - Cycle 10: Response evaluation: Immunofixation in serum. - Cycle 11: Response evaluation: Immunofixation in serum and CM in urine. - Cycle 12: Response evaluation: Serum immunofixation. - Cycle 13: Response evaluation: Immunofixation in serum. - Cycles 1 and 2: Quality of life: no questionnaire is performed.
Morales Messenguer Hospital	42	15.04.2021	Patient 351-18: The following tests stipulated by protocol were not performed: - Cycle 2: Patient Status: ECOG. - Cycles 1 and 2: Response evaluation: urine CM. - Cycle 4: Response Evaluation: Serum Immunofixation. - Cycle 5: Response Evaluation: Serum Immunofixation and Urine CM. - Cycle 6: Response evaluation: Immunofixation in urine. - Cycles 2, 5 and 6: Quality of life: no questionnaire. - Cycle 7: Quality of life: the following questions are not answered; - I feel tired - I have difficulty starting things because I am tired. - I need to sleep during the day. - Cycle 8: Quality of life: the following questions are not answered; - I feel tired. - I need to sleep during the day. - Cycle 9: Quality of life: the question "I feel fatigued" is not answered.

Morales Messenguer Hospital	43	15.04.2021	Patient 351-19: No se realizaron las siguientes pruebas estipuladas por protocolo: - Ciclo 1: Evaluación de la respuesta: Inmunofijación en orina. - Ciclos 2, 3, 5, 6 and 7: Estado del Patient: ECOG. - Ciclo 10: Calidad de vida: no se realiza el cuestionario. - Ciclos 10: Evaluación de la respuesta: CM en orina ni cuantificación de cadenas libres en suero.
Morales Messenguer Hospital	44	28.10.2021	Patient 351- 17 During the monitoring visit and in relation to the tests performed on the Patient, the following protocol deviations were detected: The following tests established in the protocol are not performed: Patient status: no ECOG performed in cycles 3 and 5. Response assessment: no urine CM measurement in cycles 2, 3, and 5 Response assessment: no urine FI in cycles 6 and 7 Quality of life: no completion of questionnaire in cycles 2 and 8
Morales Messenguer Hospital	45	15.04.2021	Patient 346-08: The following tests stipulated by protocol were not carried out: - Quality of life questionnaire: cycles 10, 14, 18, 26 and 30.
Morales Messenguer Hospital	46	13.06.2023	Patient 346-08: During the present monitoring visit, the following protocol deviations were detected: - Cycles 52, 54-56, 59, 62: No assessment of serum IF and urine IF in the - Cycle 58: No determination of serum MC, free chains and urine IF. No quality of life questionnaire is carried out. - Final visit: No assessment of plasmacytomas.
Morales Messenguer Hospital	47	15.04.2021	Patient 346-08: The following tests stipulated by protocol were not performed: - Cycle 34: Response evaluation: Immunofixation in urine. - Cycle 35: Response evaluation: Immunofixation in serum and urine. - Cycle 36: Response evaluation: Immunofixation in serum and urine and quantification of free chains in serum. - Cycles 37: Response evaluation: CM in urine, Immunofixation in serum and quantification of free chains in serum.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Canary Hospital	1	11.11.2016	Patient 354-6: According to the protocol, peripheral blood and serum samples must be sent to the reference laboratory on day 21 of Cycle 2 for the inunophenotypic characterisation of the Patient's immune status. The Study Coordinator of this centre informed the monitor that, due to forgetfulness, the samples required for day 21 of Cycle 2 of Patient 354-6 were not collected on that date. They were sent to the reference laboratory on 10 November 2016, coinciding with this Patient's C4D1.
Canary Hospital	2	11.11.2016	Patient 354-7: According to the protocol, peripheral blood and serum samples must be sent to the reference laboratory on day 21 of Cycle 2 for the inunophenotypic characterisation of the Patient's immune status. The Study Coordinator of this centre informed the monitor that, due to forgetfulness, the samples required for day 21 of Cycle 2 of Patient 354-7 were not collected on that date. They were sent to the reference laboratory on 21 November 2016, coinciding with this Patient's C4D1.
Canary Hospital	3	21.12.2016	Patient 354-7: - Medication C1: Patient starts treatment on 23 August 2016 with a dose of lenalidomide 25mg being dispensed. On 31 August 2016, after one week of treatment, the Patient developed renal failure which led to the lenalidomide dose being reduced to 15mg. By mistake, the Patient took the full 15mg blister pack, so the total dose of the cycle was 7 days of 25mg and 21 days of 15mg, making a 28-day cycle instead of 21 days.
Canary Hospital	4	21.12.2016	General No information on the dates of diagnosis is available for the relevant medical history of Patients 354-2, 354-3, 354-4, 354-6, 354-7 and 354-10. According to the protocol, during the screening period, the medical history of all included Patients should be known. The Study Coodinator comments that it is difficult to know the dates when the events occurred in another hospital and are not reflected in the current history.
Canary Hospital	5	21.12.2016	Patient 354-6: During the last monitoring visit to the Pharmacy Department, an imbalance was detected in the medication due to the dispensing of lenalidomide 15mg at C1 that did not come from the shipments made for the GEM CLARIDEX study. Said medication with batch number 14F0688, Kit 2004987 and expiry date 09/2016 was dispensed on 19 August 2016 from the GEM2014 study.
Canary Hospital	6	12.07.2017	Patient 354-14: By mistake, during cycle 2, the Patient took dexamethasome daily from day 1 to day 5 of the cycle, instead of days 1, 8, 15 and 22 as indicated in the protocol. The Patient was admitted to hospital on 20/06/2017 with a diagnosis of dysenteric syndrome, with resolution of the condition on 22/06/2017. She still remains in hospital for observation and treatment due to another AAG described as Acute renal failure. Secondary damage by Lenalidomide and myeloma-associated nephropathy cannot be ruled out.
Canary Hospital	7	21.07.2017	Patient 354-14: Patient has mistakenly consumed more doses of Lenalidomide and Dexamethasome than specified by protocol. The Patient was hospitalised with a diagnosis of Acute renal failure and was treated with dialysis. Due to this event, the study treatment was permanently discontinued. Excess lenalidomide justified the renal toxicity. Patient was discontinued from the study and started another line of treatment on 17/07/2017. She continues on dialysis.

Canary Hospital	8	25.04.2017	Patient 354-15: On 25 April 2017, the centre found a Patient candidate to enter the study who met all the inclusion criteria, and all the exclusion criteria, except one, as the Patient had Amyloidosis but of the senile cardiac type. His medical history is as follows: 72-year-old male initially admitted for heart failure and after compensation of the picture is diagnosed with symptomatic multiple myeloma IgA lambda with: - Serum CM 0.6 g/dl - AMO 72% PC - CM urine 965 mg/24h - Hb 8.5 g/dl, Cr 1.24 mg/dl, normal Ca - No lytic lesions (bone map and MRI) - Senile cardiac amyloidosis due to non-mutated transthyretin deposition leading to NYHA functional class I-II. On the other hand, he has significant bilateral osteoarthritis of the hips that causes pain and difficulty in ambulation, which is well controlled with opioids. He has had an intermittent febrile fever for 3-4 weeks without symptoms and well tolerated with high LDH which we interpret as secondary to MM". Regarding the treatment of multiple myeloma due to the heart disease and the difficulty in mobilisation, they believe that the bortezomib-based scheme (such as VMP) would not be a good option and that a Lenalidomide-Dexamethasome-type scheme, as contemplated in this clinical trial, would be a good option. For this reason, they decided to evaluate their inclusion in this study. The monitor passed the consultation to the study coordinators who, on 26 April 2017, considered that, given that Amyloidosis is a senile type (median survival of 75 months) and the grade of mild heart failure (NYHA 2: mild shortness of breath and/or angina and slight limitation during ordinary activity), he was a candidate Patient for inclusion in the study. The Patient signs the Informed Consent on 2 May 2017 and starts the screening tests.
Canary Hospital	9	04.04.2018	Patient 354-25: It was detected that Patient 354-25, on 04/04/18 coresponding to cilo 1 of treatment, was dispensed a bottle of Lenalidomide 5mg (16F1611 // 31323312) with expiry date 06/19 belonging to the GEM-CESAR study by mistake.
Canary Hospital	10	09.10.2018	Patient 354-10: Cycle 18 - Response assessment: no urine CM assessment.
Canary Hospital	11	09.10.2018	The following protocol-mandated tests were not performed: Patient 354-13: Cycle 9 - Response evaluation: CM urine. Cycle 11 - Response evaluation: Immunofixation in urine.
Canary Hospital	12	09.10.2018	The following protocol-mandated tests were not performed: Patient 354-19: Screening - Baseline examination: Ejection fraction. - Bone assessment - Diagnostic MRI imaging - PET-CT Cycle 2 - Response Evaluation: Urine CM. Cycle 5 - Response evaluation: CM urine. Progression/Relapse - AMO.

Canary Hospital	13	09.10.2018	The following protocol-mandated tests were not performed: Patient 354-25: Screening - Baseline examination: weight, height body surface area and ejection fraction. - Bone assessment - Diagnostic imaging MRI - PET-CT Cycle 1 - Response assessment: CM urine and CM serum. Final visit - Response assessment: CM urine and CM serum.
Canary Hospital	14	09.10.2018	The following protocol-mandated tests were not performed: Patient 354-29: Screening - Baseline scan: Ejection fraction. - Bone assessment - bone series.
Canary Hospital	15	01.02.2021	The following protocol-mandated tests were not performed: Patient 354-10: Cycle 26 - Response evaluation: CM serum and serum free light chains. Cycle 37 - Response evaluation: CM urine and serum free light chains.
Canary Hospital	16	01.02.2021	The following protocol-mandated tests were not performed: Patient 354-23: Screening - Baseline Scan: Ejection Fraction, Bone Assessment. Cycle 27 - Patient Status: ECOG. Cycle 28 - Patient Status: ECOG and vital signs. Cycle 29 - Patient Status: ECOG, Vital Signs; Response Assessment: CM Urine. Cycle 34 - Response Assessment: CM Urine. Cycle 31 - Response Evaluation: IF urine.
Canary Hospital	17	01.02.2021	The following protocol-mandated tests were not performed: Patient 354-36: Screening - Baseline scan: Ejection fraction. - PET-CT: Grade. Progression/Relapse - Salvage treatment: date of response to relapse treatment and date of relapse to salvage treatment.
Canary Hospital	18	05.05.2023	Patient 354-6: - No urine MC and serum free chains are not assessed in cycles 26, 27 - No urine MC is not assessed in cycle 37
Canary Hospital	19	05.05.2023	Patient 354-25: - No assessment of IFE and CM urine in the cycle 63
Canary Hospital	20	05.05.2023	Patient 354-35: - No assessment of IFE and CM urine in Cycle 23.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Vall d´Hebron Hospital	1	06.02.2017	Patient 360-1: The blood sample corresponding to C2D21 for this Patient is not sent to the assigned reference laboratory (H. Salamanca), as specified in the protocol.
Vall d´Hebron Hospital	2	06.02.2017	Patient 360-1: Analyses corresponding to C1D15 and C1D22 are not performed, as specified in the protocol. Therefore, it is not known whether the Patient had the correct haematological values at day 15 and 22 in the first treatment cycle.
Vall d´Hebron Hospital	3	06.02.2017	Patient 360-2: - Sending of biological samples: the blood sample corresponding to C2D21 for this patient was not sent to the assigned reference laboratory (Salamanca Hospital), as specified in the protocol. - Evaluation of the response: in the evaluation of the response of C3, the value of the CM in urine is not available as this sample was not analysed.
Vall d´Hebron Hospital	4	13.03.2017	Patient 360-2: During the last monitoring visit on 6 February 2017, the Pharmacy Service detected an imbalance in the medication. On 13 March 2017, the Pharmacy Department sent an email informing us of the reason for the medication discrepancy: "On 02/12/2016, a lenalidomide 15 mg kit, lot number 14F0688, expiry date 12/2016 (kit number: 2013223) not belonging to the lots sent for the study and a dexamethasome 20 mg kit from the referred study with Patient number 360-2 were supplied. However, given that the medication and dosage from both open studies is the same (same lenalidomide number and same manufacturer (celgene)), the Patient received the treatment correctly".
Vall d´Hebron Hospital	5	06.02.2017	Patient 360-4: Patient's ECOG is not determined in cycles 1 and 2. According to the protocol, it should be assessed on day 1 at the start of each treatment cycle.
Vall d´Hebron Hospital	6	06.02.2017	Patient 360-5: The Patient's ECOG is not determined at the screening visit or at C1 of treatment. According to the protocol, it should be assessed both at screening and on day 1 at the start of each treatment cycle.
Vall d´Hebron Hospital	7	15.11.2017	Patient 360-1: As specified in the protocol, at the beginning of Cycle 9 the Patient is not asked to fill in the quality of life form.
Vall d´Hebron Hospital	8	24.01.2019	Patient 360-2: - Cycles 9, 10, 13, 15, 18 and 19: Patient did not complete the Quality of Life Questionnaire - Cycle 22: Response evaluation - The following values were not obtained: serum MC, urine MC and serum free light chains.
Vall d´Hebron Hospital	9	24.01.2019	Patient 360-10: - Cycle 2: Patient did not complete the Quality of Life Questionnaire.

Vall d´Hebron Hospital	10	28.03.2019	Patient 360-10: - Selection: Diagnosis Disease - No CM performed in urine - Cycles 7, 10 and 11: Patient did not complete the Quality of Life Questionnaire.
Vall d´Hebron Hospital	11	28.03.2019	Patient 360-11: - Selection: Baseline Screening - Weight, height and ejection fraction measurements are not performed. - Cycle 4: Response assessment - No response assessment is performed. - Final Visit: - No ECOG or response assessment is performed.
Vall d´Hebron Hospital	12	28.03.2019	Patient 360-12: - Selection: ECOG is not performed.
Vall d´Hebron Hospital	13	28.03.2019	Patient 360-13: - Selection: Diagnosis Disease - No urine MC is not performed. - Screening: M.O. Aspirate - % plasma cells not performed due to AMO not diagnostic. - Cycle 12: Response Evaluation - Urine Immunofixation is not performed. - Cycles 2, 5, 6, 7, 9, 9, 10, 11 and 13: Quality of Life questionnaires are not performed.
Vall d´Hebron Hospital	14	19.08.2019	Patient 360-7: - Selection: Baseline scan - Ejection fraction is not performed.
Vall d´Hebron Hospital	15	19.08.2019	Patient 360-8: - Selection: Baseline Scan - No ejection fraction is performed - Cycle 18: Response Assessment - No response assessment is performed.
Vall d´Hebron Hospital	16	19.08.2019	Patient 360-9: - Selection: Baseline scan - Ejection fraction is not performed.
Vall d´Hebron Hospital	17	15.01.2020	The following protocol-mandated tests were not performed: Patient 360-6: - Screening: Baseline CBC - β2 Microglobulin (mg/L). - Selection: Baseline Scan - Ejection Fraction (%).
Vall d´Hebron Hospital	18	15.01.2020	The following protocol-mandated tests were not performed: Patient 360-11: - Screening: Baseline CBC - β2 Microglobulin (mg/L). - Selection: Disease at diagnosis - ECOG. - Cycle 1 - Patient Status: ECOG.
Vall d´Hebron Hospital	19	15.01.2020	The following protocol-mandated tests were not performed: Patient 360-12: - Screening: Baseline Scan - Ejection Fraction (%). - Cycle 11 - Response Assessment: Serum CM, Urine CM and Serum Free Light Chains.

Vall d´Hebron Hospital	20	15.01.2020	The following protocol-mandated tests were not performed: Patient 360-14: - Screening: Baseline Scan - Ejection fraction (%). - Final Visit - Final Visit: ECOG and vital signs.
Vall d´Hebron Hospital	21	17.11.2020	The following protocol-mandated tests were not performed: Patient 360-9: - Cycles 36-39- Patient Status: ECOG - Cycle 28- Quality of Life
Vall d´Hebron Hospital	22	17.11.2020	The following protocol-mandated tests were not performed: Patient 360-12: - Cycles 32-33- Patient Status: ECOG - Cycles 26 and 27- Quality of Life
Vall d´Hebron Hospital	23	17.11.2020	The following protocol-mandated tests were not performed: Patient 360-15: - Cycles 16- Patient Status: ECOG - Cycles 6 and 9- Quality of Life
Vall d´Hebron Hospital	24	03.06.2021	The following protocol-mandated tests were not performed: Patient 360-9: - Patient Status - cycles 40, 41, 43, 46, 48 and 49: ECOG - Quality of Life - cycles 12-14, 17-23, 26
Vall d´Hebron Hospital	25	03.06.2021	The following protocol-mandated tests were not performed: Patient 360-12: Patient Status - Cycles 34, 36, and 40-43: ECOG
Vall d´Hebron Hospital	26	28.09.2021	The following protocol-mandated tests were not performed: Patient 360-9: Cycles 50-54 - Patient Status: ECOG
Vall d´Hebron Hospital	27	28.09.2021	The following protocol-mandated tests were not performed: Patient 360-10: Cycle 14 - Quality of Life.
Vall d´Hebron Hospital	28	28.09.2021	The following protocol-mandated tests were not performed: Patient 360-15: Cycle 14 - Quality of Life
Vall d´Hebron Hospital	29	12.07.2022	The following protocol-mandated tests were not performed: Patient 360-2: Quality of Life: 21, 22, 25-34, 38, 39, 43, 44, 47 and 48

Vall d´Hebron Hospital	30	12.07.2022	The following protocol-mandated tests were not performed: Patient 360-8: Quality of life: 6,7 and 8
Vall d´Hebron Hospital	31	12.07.2022	The following protocol-mandated tests were not performed: Patient 360-9: Quality of life: 30,31 and 32
Vall d´Hebron Hospital	32	13.03.2023	The following protocol-mandated tests were not performed: Patient 360-9: Quality of life: cycles 33, 34, 36, 37, 37, 39, 41, 43, 43, 45, 46, 47, 49, 51 and 57.
Vall d´Hebron Hospital	33	13.03.2023	The following protocol-mandated tests were not performed: Patient 360-8: Quality of life: 2, 3, 11, 12, 13, 14, 15, 16 and 18.
Vall d´Hebron Hospital	34	13.03.2023	The following protocol-mandated tests were not performed: Patient 360-2: Cycles 40. Patient did not complete the Quality of Life Questionnaire.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Virgen del Rocío Hospital	1	30.11.2016	Patient 344-1: Response assessment: No data are available for light chains in the C1 response assessment. According to the Study Coordinator, such a test was requested but, due to a laboratory error, was not performed. According to the protocol, this test should be performed monthly until a complete conventional response is achieved with two determinations. The monitor reports the importance of performing this type of test from now on in order to know the response evaluation in each treatment cycle.
Virgen del Rocío Hospital	2	30.11.2016	Patient 344-2 During the monitoring visit on 30 November 2016 and in relation to the tests carried out on Patient, the following deviations from the protocol were detected: Selection: - There is no data for CM in urine. The Study Coordinator reports that the monoclonal component in urine was requested, but was not performed in the laboratory. - The relevant medical history section shows that the Patient has an allergy to Streptomycin and Metamizole, but the date of diagnosis of these pathologies is unknown. According to the protocol, this information should be reflected in the eCRD.
Virgen del Rocío Hospital	3	XX/XX/2017	Patient 344-2: - The blood sample corresponding to C2D21 for this Patient is not sent to the assigned reference laboratory (CIMA) as specified in the protocol.
Virgen del Rocío Hospital	4	XX/XX/2017	Patient 344-3: - The blood sample corresponding to C2D21 for this Patient is not sent to the assigned reference laboratory (CIMA) as specified in the protocol.
Virgen del Rocío Hospital	5	02.10.2017	Patient 344-2: The following protocol-mandated test was not performed: Final visit: ECOG not determined.
Virgen del Rocío Hospital	6	02.10.2017	Patient 344: The following test stipulated by protocol was not performed: Screening - Baseline scan: Ejection Fraction is not determined.
Virgen del Rocío Hospital	7	13.06.2018	Patient 344-1 The following protocol-mandated tests were not performed: - Cycle 2 Response evaluation: serum free light chains have not been determined. - Cycles 4, 5 and 13 Response evaluation: no determination of CM in urine.
Virgen del Rocío Hospital	8	19.06.2018	Patient 344-7 Patient 344-7 is dispensed lenalidomide and dexamethasome for cycle 1 of treatment in the outpatient area, from the pharmacy that normally attends haematology patients. The Pharmacy Service confirms that the Patient came only with the clinical report, without a prescription for clinical trials, and that the medication dispensed is commercial.
Virgen del Rocío Hospital	9	11.02.2019	Patient 344-7: Cycle 2 - response assessment: no urine CM assessment.
Virgen del Rocío Hospital	10	04.04.2019	The following protocol-mandated tests were not performed: Patient 344-3: Cycle 12 - response assessment: Serum free light chains. Cycle 14 - response evaluation: CM urine.

Virgen del Rocío Hospital	11	04.04.2019	Patient 344-4: Cycles 14 and 16 - response assessment: no urine CM assessment.
Virgen del Rocío Hospital	12	04.04.2019	The following protocol-mandated tests were not performed: Patient 344-5: Screening - Baseline scan: Ejection fraction. Bone assessment PET-CT Cycles 1 and 11 - response assessment: CM urine. Cycle 2 - response assessment: CM urine and serum free light chains. Cycle 6 - response evaluation: CM urine, serum immunofixation and serum free light chains.
Virgen del Rocío Hospital	13	04.04.2019	The following protocol-mandated tests were not performed: Patient 344-6: Cycle 9 - response evaluation: CM urine. Cycle 10 - response evaluation: CM urine, Immunofixation in serum and serum free light chains.
Virgen del Rocío Hospital	14	04.04.2019	The following protocol-mandated tests were not performed: Patient 344-8: Screening - PET-CT
Virgen del Rocío Hospital	15	10.02.2020	The following protocol-mandated tests were not performed: Patient 344-1: Cycle 14 - response assessment: CMo
Virgen del Rocío Hospital	16	10.02.2020	The following protocol-mandated tests were not performed: Patient 344-4: Screening - Baseline Scan: Ejection Fraction.
Virgen del Rocío Hospital	17	11.08.2020	The following protocol-mandated tests were not performed: Patient 344-1: Cycle 15: Patient Status: ECOG. Cycle 5: Response evaluation: CM in urine.
Virgen del Rocío Hospital	18	11.08.2020	The following protocol-mandated tests were not performed: Patient 344-3: Cycle 42: Patient Status: ECOG and Vital Signs
Virgen del Rocío Hospital	19	11.08.2020	The following protocol-mandated tests were not performed: Patient 344-4: Cycles 34, 35 and 36: Patient Status: ECOG. Cycles 41 and 42: Patient Status: ECOG. Cycles 42 and 43: Response evaluation: CM in serum and urine, Oligoclonal bands and free light chains in serum.
Virgen del Rocío Hospital	20	11.08.2020	The following protocol-mandated tests were not performed: Patient 344-7: Cycle 16: Patient Status: ECOG.
Virgen del Rocío Hospital	21	19.11.2020	The following protocol-mandated tests were not performed: Patient 344-3: Cycle 46: Patient Status: ECOG. Cycle 48: Patient Status: Vital Signs.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Princess's Hospital	1	2/16/2017	Patient 355-1: Response assessment: No light chain information is available at the time of screening. In addition, there are no values for urine CM or light chains in the evaluation of the C1 and C2 response. The monitor reminds us that this test is essential to know the disease and to be able to monitor it. From the center, the CS comments that the tests are requested, however, it is the local laboratory that does not perform the quantification of the test. The CS undertakes to insist on obtaining these results in successive cycles.
Princess's Hospital	2	2/16/2017	Patient 355-2: Response assessment: No urine MC data are available at the time of screening or in the C1 response assessment. In addition, there are no values for light chains or urine MC in the evaluation of the C2, C3 and C4 response. The monitor reminds us that this test is essential to know the disease and to be able to monitor it. From the center, the CS comments that the tests are requested, however, it is the local laboratory that does not perform the quantification of the test. The CS undertakes to insist on obtaining these results in successive cycles.
Princess's Hospital	3	2/16/2017	Patient 355-3: Response assessment: No urine MC data are available at the time of screening or in the C1 response assessment. In addition, there are no values for light chains or urine MC in the C2 response assessment. In addition, there is no information on the Patient's height at the time of screening, as indicated in the study protocol. The monitor reminds us that knowing the CM in urine at the different times established by the protocol is fundamental to know the disease and to be able to follow it up. From the center, the CS comments that the tests are requested, however, it is the local laboratory that does not perform the quantification of the same. The CS undertakes to insist on obtaining these results in successive cycles.
Princess's Hospital	4	5/20/2019	Patient 355-1: Final visit: no determination of ECOG and CM in urine.
Princess's Hospital	5	5/20/2019	Patient 355-9: - Selection: the ECOG is not determined and the years of diagnosis are not indicated for the following events: HT, type II DM, diabetic retinopathy, renal failure, and S1 lesion, L3-L4 hernia. - Cycle 1: neither ECOG nor urine CM is determined. - Cycle 2: no determination of ECOG and CM in urine or serum free light chains. - Cycle 3: neither ECOG nor MC in urine is determined. - Cycle 4: CM in urine is not determined. - Cycle 6 and 7: serum MC is not determined.
Princess's Hospital	6	5/20/2019	Patient 355-11: - Screening: no determination of MC in urine or years of diagnosis of the following events: HT, type II DM, hyperlipidemia and subclinical hyperthyroidism. - Cycles 1 and 2: neither serum MC nor urine MC is determined, nor does the Patient complete the quality of life questionnaire. - Cycles 3 and 4: ECOG is not determined.
Princess's Hospital	7	6/25/2020	Patient 355-1: - Selection: Disease at diagnosis: serum free light chains are not determined. - Cycle 27: Response evaluation: serum free light chains are not determined. - Cycle 28: Response evaluation: no determination of CM in urine.

Princess's Hospital	8	6/25/2020	Patient 355-2: Cycle 27: Response assessment: no determination of MC in urine.
Princess's Hospital	9	6/25/2020	Patient 355-3: Cycles 11 and 12: Response evaluation: no serum free light chains are determined.
Princess's Hospital	10	6/25/2020	Patient 355-4: - Cycle 1: Response evaluation: no determination of CM in urine. - Cycles 2 and 4: Response evaluation: no determination of CM in urine or serum free light chains. - Cycle 3 and 7: Response evaluation: serum free light chains are not determined. - Cycle 5 and 6: Response evaluation: serum free light chains and urine immunofixation are not determined.
Princess's Hospital	11	6/25/2020	Patient 355-6: - Ciclos 1, 4, 5: Evaluation of the response: immunofixation in urine and free chains in serum are not determined. - Cycles 2, 8, 12, 15, 26: Response evaluation: urine immunofixation is not determined. - Cycles 16, 17, 20, 22- 25, 36 and 38: Evaluation of the response: CM in urine is not determined. - Cycle 31: Response evaluation: serum immunofixation is not determined. - Cycle 32: Response evaluation: serum and urine immunofixations are not determined. - Cycle 37: Response evaluation: no assay is performed this cycle due to COVID-19 prevention.
Princess's Hospital	12	6/25/2020	Patient 355-9: - Cycles 9 and 19: Response evaluation: urine immunofixation is not determined. - Cycle 11: Quality of life: form not completed. - Cycle 14: Response evaluation: serum immunofixation is not determined. - Cycle 15: Response evaluation: no serum or urine immunofixation determined. - Cycle 20: Evaluation of the response: no analysis is performed this cycle due to COVID-19 prevention.
Princess's Hospital	13	6/25/2020	Patient 355-11: - Cycles 5-11: Patient Status: ECOG is not determined. Cycles 4, 5 and 12: Response evaluation: urine immunofixation is not determined. - Cycle 8: Response evaluation: serum free light chains are not determined. - Cycles 9 and 10: Response evaluation: immunofixation in serum and urine are not determined.
Princess's Hospital	14	10/28/2020	Patient 355-1: Cycle 25: Quality of life: questionnaire. Patient 355-2: Cycle 5: Quality of life: questionnaire. Patient 355-3: Cycles 5, 9, 11, 12 and 13: Quality of life: questionnaire.
Princess's Hospital	15	4/7/2021	Patient 355-6: - Cycle 31: Patient Status: no ECOG performed - Cycle 12: Response evaluation: no urine immunofixation quantified.
Princess's Hospital	16	4/7/2021	Patient 355-11: - Cycle 5: Response evaluation: no CM quantified in urine - Cycle 10: Response evaluation: no Immunofixation quantified in either serum or urine.
Princess's Hospital	17	5/18/2022	Patient 355-6: - ECOG-ciclos: 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16
Princess's Hospital	18	10/24/2022	Patient 355-6: - Quality of life: Cycles 1-3, 37 - Response evaluation: Cycles 36, 37 (urine), Cycles 30, 37, 43 - Patient Status: Cycles 37, 46, 49, 49, 53 45, 47, 50, 51, 52 (ECOG)

Princess's Hospital	19	4/19/2023	Patient 355-9: - Cycle 5,7 and 35: No ECOG is performed - Cycle 35: No evaluation of the Patient's response is performed in this cycle.
Princess's Hospital	20	4/19/2023	Patient 355-1: - Cycle 28 and 29: No ECOG - Cycle 29: No determination of CM in urine.
Princess's Hospital	21	4/19/2023	Patient 355-4: - Cycle 2,5 and 6: Patient Status: No ECOG performed - Final visit: Response assessment: No serum free light chains determined.
Princess's Hospital	22	3/19/2023	Patient 355-6: Cycle 5,6,9,10,11,12,13,15,16: ECOG is not performed.
Princess's Hospital	23	3/19/2023	Patient 355-3: Cycle 13: ECOG is not performed.
Princess's Hospital	24	3/19/2023	Patient 355-3: - Selection: In the diagnostic disease assessment, serum free chain values were not measured - Cycle 7: ECOG was not performed.
Princess's Hospital	25	3/19/2023	Patient 355-5: Final visit: ECOG is not carried out.
Princess's Hospital	26	3/19/2023	Patient 355-6: Cycle 3,7,8,14; ECOG is not performed.
Princess's Hospital	27	4/19/2023	Patient 355-7: Final visit: No determination of MC in urine.
Princess's Hospital	28	4/19/2023	Patient 355-8: Bone assessment is not performed.
Princess's Hospital	29	4/19/2023	Patient 355-9: - Final visit: No ECOG is performed - Cycle 20 and 23: In the response assessment, urine MC and light chains are not measured.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Germans Trias i Pujol Hospital	1	10/20/2017	Patient 346-2: The following protocol-required tests are not determined: - Screening: Baseline Scan: Ejection Fraction and PET-CT: Number of lesions. - Cycle 1: Response evaluation: Immunofixation in urine, oligoclonal bands and serum free light chains.
Germans Trias i Pujol Hospital	2	11/14/2018	Patient 346-7: - Cycle 1: The section "I am able to do my usual activities" of the Quality of Life questionnaire has not been completed.
Germans Trias i Pujol Hospital	3	10/20/2017	The following protocol-mandated tests were not performed: Patient 346-8: - Cycle 1: response evaluation: urine immunofixation, oligoclonal bands and serum free light chains. - Cycle 2: response evaluation: urine immunofixation, oligoclonal bands and serum free light chains. - Cycle 3: response evaluation: immunofixation in urine, oligoclonal bands and serum free light chains. - Cycle 4: response evaluation: immunofixation in urine, oligoclonal bands and serum free light chains.
Germans Trias i Pujol Hospital	4	1/2/2020	The following protocol-mandated tests were not performed: Patient 346-3: - Cycles 5 and 6 - Response Evaluation: Immunofixation in urine and Free light chains in serum.
Germans Trias i Pujol Hospital	5	1/2/2020	Patient 346-4: - Screening - Baseline CBC: Calcium corrected - Final visit - Response assessment: not assessed because Patient dies.
Germans Trias i Pujol Hospital	6	1/2/2020	The following protocol-mandated tests were not performed: Patient 346-5: - Cycle 4 - Response Evaluation: Immunofixation in urine. - Cycles 2 and 4 - Response Evaluation: Serum free light chains.
Germans Trias i Pujol Hospital	7	1/2/2020	The following protocol-mandated tests were not performed: Patient 346-9: Cycles 3 through 8, 10 and 11 - Response evaluation: serum free light chains.
Germans Trias i Pujol Hospital	8	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-13: - Screening - Baseline scan: ejection fraction (%). - Cycles 1 to 6 - Response evaluation: serum free light chains.
Germans Trias i Pujol Hospital	9	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-14: - Screening - Baseline scan: ejection fraction (%). - Cycle 1 - Response Evaluation: CM in urine and serum free light chains. - Cycles 3, 4, 5 and 8 - Response Evaluation: CM in urine at 24h.

Germans Trias i Pujol Hospital	10	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-16: - Screening - Baseline Scan: ejection fraction (%). - Final Visit - Final Visit: ECOG. - Cycles 2, 3 and 4 - Patient Status: ECOG. - Cycles 2, 3 and 4 - Response Evaluation: Serum free light chains. - Cycle 4 - Response Evaluation: Immunofixation in urine.
Germans Trias i Pujol Hospital	11	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-17: - Cycles 1 through 6, 8 and 12 through 15, 17 and 18 - Response evaluation: Serum free light chains. - Cycles 4, 5, 6, 12, 13, 15, 17 and 18 - Response evaluation: Immunofixation in urine. - Cycles 14, 15, 17 and 18 - Response evaluation: Immunofixation in serum. - Cycle 10 - Response evaluation: CM in urine.
Germans Trias i Pujol Hospital	12	1/2/2020	The following protocol-mandated tests were not performed: Patient 346-18: - Screening - Baseline scan: ejection fraction (%). - Cycles 1, 2, 3, 4, 6, 6, 8, 10, 13 and 14 - Response evaluation: Serum free light chains. - Cycles 4 and 13 - Response evaluation: Immunofixation in urine. - Cycles 4, 10 and 14 - Response evaluation: Immunofixation in serum. - Cycles 1, 8 and 10 - Response evaluation: CM in urine.
Germans Trias i Pujol Hospital	13	1/2/2020	The following protocol-mandated tests were not performed: Patient 346-19: - Selection - Baseline CBC: Calcium corrected and Albumin. - Selection - Baseline Exam: Weight, Height, Electrocardiogram and Ejection Fraction (%).
Germans Trias i Pujol Hospital	14	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-20: - Cycles 1, 7, 8 and 9 - Response evaluation: serum free light chains. - Cycles 1, 2, 7 and 8 - Response evaluation: Immunofixation in urine. - Cycles 8 and 9 - Response evaluation: Immunofixation in serum. - Cycle 9 - Response evaluation: CM in urine.
Germans Trias i Pujol Hospital	15	8/5/2020	Patient 346-10: Final visit: Response evaluation: no immunofixation in serum and urine and free light chains in serum.
Germans Trias i Pujol Hospital	16	8/5/2020	The following tests stipulated by protocol were not performed: Patient 346-11: - Screening: Disease at diagnosis: CM in urine and serum free light chains. - Cycle 5: Response evaluation: Oligoclonal bands and serum free light chains. - Cycles 10 and 13: Response evaluation: Immunofixation in urine. - Cycles 15, 18, 19 and 21-24: Response evaluation: Immunofixation in urine, oligoclonal bands and serum free light chains. - Cycle 25: Response evaluation: Immunofixation in urine and serum free light chains.

Germans Trias i Pujol Hospital	17	8/5/2020	The following tests stipulated by protocol were not performed: Patient 346-14: - Cycle 2: Response evaluation: urine CM, oligoclonal bands and serum free light chains. - Cycle 8: Response evaluation: Serum free light chains. - Cycle 10: Response evaluation: Immunofixation in urine, oligoclonal bands, serum free light chains.
Germans Trias i Pujol Hospital	18	8/5/2020	The following tests stipulated by protocol were not performed: Patient 346-15: Cycles 1-6, 8-11: Response evaluation: oligoclonal bands, serum free light chains.
Germans Trias i Pujol Hospital	19	8/5/2020	The following tests stipulated by protocol were not performed: Patient 346-16: Cycle 1: Patient Status: ECOG.
Germans Trias i Pujol Hospital	20	12/16/2020	The following tests stipulated by protocol were not performed: Patient 346-2: Response evaluation: - Cycle 23: Serum immunofixation, Urine immunofixation and oligoclonal bands. - Cycles 24-25, 27, 28, 30, 33 and 35-36: Serum immunofixation, urine immunofixation, oligoclonal bands and serum free light chains. - Cycle 34: serum free light chains. Quality of life: - Cycles 8 and 11.
Germans Trias i Pujol Hospital	21	12/16/2020	The following protocol-mandated tests were not performed: Patient 346-5: Screening: - Baseline Scan: ejection fraction (%). - Relevant Medical History: year of diagnosis. V. Final: - Response Evaluation: urine immunofixation, oligoclonal bands and serum free light chains. Progression/Recline: - M.O. aspirate.
Germans Trias i Pujol Hospital	22	12/16/2020	The following tests stipulated by protocol were not performed: Patient 346-12: Screening: Baseline Scan: ejection fraction (%). Response evaluation: - Cycles 14-16, 19-23, 25, 27 and 29: Serum immunofixation, Urine immunofixation and oligoclonal bands. - Cycles 17, 18, 24 and 28: Serum immunofixation, urine immunofixation, oligoclonal bands and serum free light chains. - Cycle 26: Immunofixation in urine. Quality of life: Cycle 11.
Germans Trias i Pujol Hospital	23	5/5/2021	The following tests stipulated by protocol were not performed: Patient 346-2: Response evaluation: Cycles 38-40: Immunofixation in serum, Immunofixation in urine, oligoclonal bands and free light chains in serum.

Germans Trias i Pujol Hospital	24	5/5/2021	The following tests stipulated by protocol were not performed: Patient 346-2: Response evaluation: - Cycle 30: Serum immunofixation and Urine immunofixation. - Cycle 32: Immunofixation in serum, Immunofixation in urine, oligoclonal bands and free light chains in serum.
Germans Trias i Pujol Hospital	25	5/5/2021	The following tests stipulated by protocol were not performed: Patient 346-17: Screening: - Diagnostic disease: urine CM. - Baseline examination: ejection fraction. - PET-CT. Final visit: - Plasmacytomas: transverse size and axial size. Response evaluation: - Cycles 21 and 22: Immunofixation in urine, oligoclonal bands and free light chains in serum.
Germans Trias i Pujol Hospital	26	5/5/2021	The following tests stipulated by protocol were not performed: Patient 346-17: Response evaluation: - Cycle 23: CM urine, urine immunofixation, oligoclonal bands and serum free light chains. - Cycle 24: CM urine, urine immunofixation, oligoclonal bands and serum free light chains.
Germans Trias i Pujol Hospital	27	1/2/2020	The following tests stipulated by protocol were not performed: Patient 346-20: Response evaluation: - Cycle 13: CM urine - Cycles 14: CM urine, serum immunofixation, and serum free light chains. - Cycle 15: Serum immunofixation, serum free light chains.
Germans Trias i Pujol Hospital	28	4/3/2023	The following tests stipulated by protocol were not performed: Patient 346-2: Response evaluation: - Cycle 19: serum free light chains. - Cycle 43: serum free light chains.
Germans Trias i Pujol Hospital	29	4/3/2023	The following tests stipulated by protocol were not performed: Patient 346-12: Response evaluation: - Cycles 1: serum free light chains. - Cycles 5: serum free light chains. - Cycle 8: serum free light chains. - Cycle 31: immunofixation in serum, immunofixation in urine and free light chains in serum. - Cycle 33: serum free light chains. - Cycle 42: serum immunofixation, urine immunofixation, oligoclonal bands and serum free light chains.

Germans Trias i Pujol Hospital	30	9/28/2023	The following protocol-mandated tests were not performed: <u>Patient 346-18:</u> - Cycles 15 - Response evaluation: Urine immunofixation and oligoclonal bands. - Cycles 16, 17, 18, 20 and 23 - Response evaluation: Urine immunofixation, oligoclonal bands and serum free chains. - Cycles 1 and 12 - Response evaluation: Immunofixation in serum, oligoclonal bands and free chains in serum. - Cycles 19 - Response evaluation: Immunofixation in urine and serum free chains. - Cycles 21.- Evaluation of the response: Immunofixation in urine, immunofixation in serum and oligoclonal bands. - Evaluation of the response: Immunofixation in urine, immunofixation in serum, oligoclonal bands and free chains in serum.
Germans Trias i Pujol Hospital	31	9/28/2023	The following tests stipulated by protocol were not performed: <u>Patient 346-20:</u> - Cycle 10: immunofixation in serum and urine, oligoclonal bands and serum free light chains. - Cycle 11: immunofixation in serum and urine, oligoclonal bands and serum free light chains. - Cycle 15: immunofixation in serum and serum free light chains. - Cycle 17: immunofixation in serum and urine, oligoclonal bands and serum free light chains.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Santiago de Compostela University Hospital	1	4/6/2017	Patient 354-5: - C4 medication: Patient begins treatment on August 19, 2016 dispensing one bottle of lenalidomide 25mg. As of November 11, 2016, the date Patient begins C4, The pharmacy service dispenses one bottle of lenalidomide 25mg lot 14F0033 expiration date 08/2016. As of November 16, 2016 and after perceiving the error on the medication expirations, a new container of lenalidomide 25mg lot 15F1723 with expiration date 6/17 is dispensed and the leftover expired medication (15 units) is removed. Therefore, the doses between November 11 and November 16, 2016 correspond to lot 14F0033 expired since August 2016. However, no adverse event has been perceived in this period or subsequently that could have originated from this error. The monitor recalls the importance of separating expired medication and immediately notifying the CRO of this type of event.
Santiago de Compostela University Hospital	2	4/28/2017	Patient 345-1: At Patient 345-1's D1C6 visit, Patient 345-1 was scheduled to take the dexamethasome 40 mg trial on the same day of the visit on 04/28/17. However, due to an error the Patient took the dexamethasome 40 mg the day before (04/27/17) and therefore on 04/28/17 as recorded in the clinical course the Patient did not take the corresponding dose of dexamethasome.
Santiago de Compostela University Hospital	3	4/28/2017	Patient 354-1: The Patient mistakenly took on April 27, 2017 the dose of Dexamethasome corresponding (5 tablets of 8mg) to the day of April 28, 2017. He has not referred any adverse event due to this error. The monitor transfers this deviation to the study coordinators who, on April 28, 2018, indicate that there is no problem due to this error in the intake.
Santiago de Compostela University Hospital	4	9/13/2018	Patient 345-1: Cycle 5: no MC is determined in urine.
Santiago de Compostela University Hospital	5	9/13/2018	Patient 345-3: – Cycle 1: No determination of oligoclonal bands in Patient - Cycles 1 and 2: No determination of CM in urine.
Santiago de Compostela University Hospital	6	9/13/2018	Patient 354-5: – Cycle 6: No determination of CM in urine - Cycles 10, 17, 22 and 23: No determination of ECOG.
Santiago de Compostela University Hospital	7	3/25/2019	The following protocol-mandated tests were not performed: Patient 345-3: - Cycle 3, cycle 5, cycle 7 to cycle 10 - response evaluation: CM in urine. - Cycle 4 - response evaluation: CM in urine and serum free light chains. - Cycle 6 - response evaluation: CM in urine and oligoclonal bands. - Cycle 14 - Patient status: ECOG.
Santiago de Compostela University Hospital	8	3/25/2019	The following tests stipulated by protocol were not performed: Patient 354-5: - Cycle 6 - response assessment: serum CM. - Progression/Relapse: AMO. - Screening: Baseline scan: ejection fraction.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Gregorio Marañón Hospital	1	5/14/2019	Patient 731-1: Selection: Ejection fraction is not determined.
Gregorio Marañón Hospital	2	5/14/2019	Patient 731-2: Selection: No determination of Ejection Fraction - Cycle 2: No determination of serum CM
Gregorio Marañón Hospital	3	11/14/2019	Patient 731-2: Cycle 7: sFLC-kappa and sFLC-lambda are not determined.
Gregorio Marañón Hospital	4	9/10/2020	Patient 731-1: - Cycle 17: vital signs, haematological and biochemical values are not determined. - Cycle 16: response assessment is not determined.
Gregorio Marañón Hospital	5	9/10/2020	Patient 731-2: - Cycle 15- response assessment is not determined - Cycles 16, 18 and 19- serum free light chains not determined.
Gregorio Marañón Hospital	6	6/15/2021	Patient 731-1: Cycle 27- Patient's status: ECOG not determined.
Gregorio Marañón Hospital	7	6/15/2021	Patient 731-2: Cycle 15, 17, 27, 27, 29 and 30- Patient's status: ECOG not determined.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Valencia Clinic Hospital	1	5/9/2019	General - As of 09/05/2019, during the monitoring visit to the Pharmacy Service, it was detected that, although the dispensing of Fortecortin 40 mg was being carried out with the full pack, Patient 732-1 does not comply well with the medication during the first 3 cycles due to only taking it for 3 weeks instead of 4, as described in the protocol.
Valencia Clinic Hospital	2	5/9/2019	Patient 732-1: - Cycles 2 and 3: No determination of MC in urine.
Valencia Clinic Hospital	3	7/29/2020	Patient 732-1: - Cycles 4 -15, 17 and 18: Response evaluation: No urine immunofixation.
Valencia Clinic Hospital	4	5/19/2021	Patient 732-1: - Cycles 26-28: Patient Status: No ECOG performed - Cycle 20: Response assessment no urine CM performed.
Valencia Clinic Hospital	5	11/2/2022	Patient 732-1: - Cycles 30 and 37: Patient Status: No ECOG performed - Cycle 36: Response assessment no serum MC or urine MC enhanced
Valencia Clinic Hospital	6	1/30/2023	Patient 732-1: - Cycle 34: response evaluation: oligoclonal bands are not assessed. - Cycle 37: Patient's status: ECOG assessment is not performed. - Cycle 38, 39, 42, 43, 43, 44, 45: response evaluation: no urine CM is determined. - Cycle 35, 40, 41: response evaluation: no CM in serum or CM in urine.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Txagolrrittxu Hospital	1	1/24/2019	Patient 735-1: Cycle 1 - Medication: Dexamethasome 4 mg from the study is not dispensed, another brand name is given in error.
Txagolrrittxu Hospital	2	1/24/2019	Patient 735-1: Screening - Baseline CBC: LDH is not determined. - Disease at diagnosis: ECOG, serum MC and urine MC are not determined. - Baseline examination: No physical examination, no weight, no height, no ejection fraction. Cycle 1 - Patient Status: No ECOG or CM serum. Cycle 2 - Patient Status: No ECOG or serum CM is performed. Cycle 3 - Patient Status: No ECOG is performed.
Txagolrrittxu Hospital	3	1/24/2019	Patient 735-2: Selection - Disease at diagnosis: ECOG is not determined. - Baseline examination: Weight, height and ejection fraction are not performed. Cycle 1 - Patient Status: No ECOG or urine CM is performed. Cycle 2 - Patient Status: ECOG is not performed.
Txagolrrittxu Hospital	4	1/24/2019	Patient 735-3: Selection - Disease at diagnosis: ECOG and CM urine are not determined. - Baseline examination: Weight, height and ejection fraction are not performed. Cycle 1 - Patient's condition: ECOG is not performed.
Txagolrrittxu Hospital	5	7/15/2019	Patient 735-1: Cycle 3 - Patient Status: ECOG and vital signs are not performed. ¬ Response evaluation: No urine CM is determined. Cycle 4 - Patient Status: No ECOG or vital signs are performed. ¬ Response evaluation: No serum CM or urine CM determined. Cycle 5 - Patient Status: ECOG and vital signs are not performed. Cycle 6 - Patient Status: ECOG and vital signs are not performed. Cycle 7 - Patient Status: No ECOG or vital signs are performed. Cycle 8 - Patient Status: No ECOG or vital signs are performed. ¬ Response evaluation: No urine CM is determined. Cycle 9 - Patient Status: ECOG and vital signs are not performed.

Txagolrrittxu Hospital	6	7/15/2019	Patient 735-2: Cycle 3 - Response Evaluation: urine CM is not determined. Cycle 4 - Patient Status: ECOG and vital signs are not performed. - Response Evaluation: No urine MC determined. Cycle 5 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 6 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 7 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 8 - Patient Status: No ECOG or vital signs are performed.
Txagolrrittxu Hospital	7	7/15/2019	Patient 735-3: Cycle 1 - Patient Status: No ECOG or vital signs are performed. Cycle 2 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine CM is determined. Cycle 3 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 4 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 5 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 6 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 7 - Patient Status: No ECOG or vital signs are performed.
Txagolrrittxu Hospital	8	7/15/2019	Patient 735-4: Selection - Disease at diagnosis: ECOG is not determined. - Baseline examination: Weight, height and ejection fraction are not performed. Cycle 1 - Patient Status: ECOG and vital signs are not performed. - Response assessment: Urine MC is not determined. Cycle 2 - Patient Status: ECOG and vital signs are not performed. - Response Evaluation: No urine MC is determined. Cycle 3 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 4 - Patient Status: No ECOG or vital signs are performed. - Response Evaluation: No urine MC is determined. Cycle 5 - Patient Status: No ECOG or vital signs are performed.

Txagolrrittxu Hospital	9	12/5/2019	Patient 735-1: Cycle 9 - Response Evaluation: No urine CM is determined. Cycle 10 - Patient Status: ECOG is not performed. Response Evaluation: No urine CM determined. Cycle 11 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 12 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 13 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 14 - Patient Status: No ECOG performed.
Txagolrrittxu Hospital	10	12/5/2019	Patient 735-2: Cycle 9 - Patient Status: ECOG is not performed. Response Evaluation: No urine CM is determined. Cycle 10 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 11 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 12 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 13 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 14 - Patient Status: No ECOG performed.
Txagolrrittxu Hospital	11	12/5/2019	Patient 735-3: Cycle 7 - Response Evaluation: No urine CM is determined. Cycle 8 - Patient Status: ECOG is not performed. Response Evaluation: No urine CM determined. Cycle 9 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 10 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 11 - Patient Status: No ECOG performed. Response Evaluation: No urine MC determined.

Txagolrrittxu Hospital	12	12/5/2019	Patient 735-4: Cycle 5 - Response Evaluation: No urine CM is determined. Cycle 6 - Patient Status: ECOG is not performed. Response Evaluation: No urine CM determined. Cycle 7 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 8 - Patient Status: No ECOG performed. Response Evaluation: No urine MC determined. Cycle 9 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 10 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 11 - Patient Status: No ECOG performed.
Txagolrrittxu Hospital	13	10/20/2020	The following protocol-mandated tests are not determined: Patient 735-1 Cycle 14 and 15 - Response Evaluation: Urine CM. Cycle 15 and 16 - Patient Status: ECOG. Cycle 16 - Response evaluation: Serum MC, urine MC and serum free light chains. Final visit - ECOG, serum MC, urine MC and serum free light chains. Patient 735-2 Cycle 14 to 18 and cycle 20 to 25 - Response evaluation: ECOG. Cycle 15, 16, 17, 19, 20, 20, 21, 22 and 24 - Response evaluation: CM in urine. Cycle 18 - Response evaluation: serum CM, urine CM and serum free light chains. Cycle 23 - Response evaluation: CM in urine and serum free light chains. Cycle 20, 21 and 23 - Quality of life. Patient 735-3 Cycle 13, 14 and 15 - Response evaluation: CM in urine. Cycles 14 through 21 - Patient Status: ECOG. Response Evaluation: No urine CM determined. Cycle 15, 16, 17 and 20 - Quality of Life. Patient 735-4 Final Visit - Plasmacytomas: Transverse size and axial size. - Final visit: ECOG - Response Evaluation: Urine CM.
Txagolrrittxu Hospital	14	4/21/2021	The following protocol-mandated tests were not performed: Patient 735-2: Cycles 26 through 29 - Response evaluation: ECOG. Cycles 25 to 28 - Response evaluation: CM in urine.

Txagolrrittxu Hospital	15	4/21/2021	The following protocol-mandated tests were not performed: <u>Patient 735-3:</u> Cycles 23, 25 and 27 - Patient Status: ECOG. Cycles 11 through 18, 20, 22 and 26 - Response evaluation: urine CM. Cycle 24 - Response evaluation: CM in urine and blood. Cycles 22, 24, 25, 26 and 27- Quality of life. Cycles 21 and 23- Quality of life questions: o I feel down ("dragged down"). o I have difficulty getting things started because I am tired. o I have difficulty finishing things because I am tired o I am too tired to eat
Txagolrrittxu Hospital	16	12/5/2019	The following protocol-mandated tests were not performed: <u>Patient 735-2:</u> Cycle 9 - Patient Status: ECOG not performed. Response Evaluation: No urine CM determined. Cycle 10 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 11 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 12 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 13 - Patient Status: No ECOG performed. Response Evaluation: No urine CM determined. Cycle 14 - Patient Status: No ECOG performed.
Txagolrrittxu Hospital	17	8/26/2022	The following tests stipulated by protocol were not performed: <u>Patient 731</u> -Cycle 1-Medication: per pharmacy records took commercial dexamethasome. <u>Patient 735-3</u> -Patient's status: 34, 36, 38, 39, 41, 42 -ECOG: Cycles 33, 35, 37, 39, 40, 43 -CM urine: cycle 39, 42 -Evaluations of response not performed: 33, 35, 37, 37, 38, 40, 40, 41 -Quality of life: cycle 34, 36, 38, 39, 41, 41, 42
Txagolrrittxu Hospital	18	2/23/2023	<u>Patient 735-1:</u> - No response assessment is performed in cycles 43, 44, 45, 46 and final visit. - Patient status and ECOG are not determined in cycles 43, 44, 45, 46. - Quality of life questionnaire is not performed in cycles 44, 45 and 46. - Plasmacytomas are not determined in the final visit. The Patient comes to the center every two cycles by decision of the Principal Investigator, and the last cycle coincides with a SAE..

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Marqués de Valdecilla Hospital	1	6/29/2023	Patient 736-1: - Selection: Patient 736-01's ejection fraction measurement at the screening visit was requested by the center in order to be able to include the Patient in the study. It was found to be correct and therefore the Patient met the inclusion criteria. However, the numerical value is not given so the value collected in the eCRD is not found. - Cycle 15: In the visit corresponding to this cycle of Patient 736-01 the evaluation of the response is not carried out because Patient leaves the study due to disease progression.
Marqués de Valdecilla Hospital	2	6/29/2023	Patient 736-2: - Selection: The measurement of Patient 736-02's ejection fraction at the screening visit was requested by the center in order to include the Patient in the study. It was found to be correct and therefore the Patient met the inclusion criteria. However, the numerical value is not given, so that the value recorded in the eCRD is not found.
Marqués de Valdecilla Hospital	3	6/29/2023	Patient 736-3: - Selection: Patient 736-03's ejection fraction measurement at the screening visit was requested by the center in order to be able to include the Patient in the study. It was found to be correct and therefore the Patient met the inclusion criteria. However, the numerical value is not given, so that the value recorded in the eCRD is not found.
Marqués de Valdecilla Hospital	4	6/29/2023	Patient 736-2: On 01/04/2019 Patient 736-2 is prescribed a weekly dose of dexamethasome 40mg (which would correspond to 20 tablets of dexamethasome 8mg). However, 20 tablets of Dexamethasome 4mg Batch E200894 (weekly dose of 20mg) are dispensed to Patient from the Pharmacy.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
Jerez Hospital	1	7/11/2019	Patient 738-2: At the beginning of cycle 4 (08/01/2019) Patient presents neutropenia, for which reason the PI prescribes lenalidomide 15mg per day, this reduction from 25mg to 15mg remains for the first 7 days of the cycle. After these 7 days (01/15/2019), the PI increases the dose back to 25mg until the end of the cycle (14 days). However, Patient mistakenly takes 16 days of lenalidomide 25mg, in addition to the 7 days he had taken lenalidomide 15mg. The PI documents this deviation in the medical record following the tablet count on the day Patient comes in for consultation for the start of cycle 5 (06/02/2019). During the monitoring visit, the CRA confirms this deviation after counting the medication returned by the Patient. - Total dose prescribed for cycle 4: 355mg. - Total dose taken by Patient in Cycle 4: 405mg The Patient does not reach the maximum lenalidomide dose stipulated by protocol (525mg), so it is not a serious deviation.
Jerez Hospital	2	9/2/2020	The following protocol-mandated tests were not performed: Patient 738-1: Screening: Baseline scan: ejection fraction. Cycles 8, 15, 20, 21 and 22: Patient Status: ECOG. Cycles 5 and 9: Response evaluation: CM in urine. Cycles 2, 19, 20, 20, 21 and 23: Quality of life: no form performed.
Jerez Hospital	3	9/2/2020	The following protocol-mandated tests were not performed: Patient 738-2: Screening: Baseline scan: height. Final visit: Final visit: ECOG Cycles 1, 11 and 19: Patient's Status: ECOG Cycles 5 and 7: Response evaluation: CM in urine. Cycles 2: Quality of life: no form performed.
Jerez Hospital	4	9/2/2020	The following protocol-mandated tests were not performed: Patient 735-3: Screening: Baseline scan: ejection fraction. Final visit: Final visit: ECOG. Cycles 2, 6, 10, 13 and 15: Patient Status: ECOG. Cycle 3: Response evaluation: CM in urine. Cycles 7, 10 and 11: Response evaluation: CM in serum and serum free light chains.
Jerez Hospital	5	9/2/2020	The following protocol-mandated tests were not performed: Patient 735-4: Screening: Baseline scan: electrocardiogram. Cycles 12, 14, 15 and 16: Patient Status: ECOG. Cycles 12, 13, 14 and 15: Quality of life: no form performed.

Jerez Hospital	6	3/23/2021	The following protocol-mandated tests were not performed: Patient 738-1: Cycles 24, 26-28: Patient Status: ECOG. Cycle 24: Response assessment: urine CM. Cycles 24, 27-28: Quality of life: no form performed.
Jerez Hospital	7	3/23/2021	The following protocol-mandated tests were not performed: Patient 735-4: Cycles 19-24: Patient Status: ECOG. Cycles 19, 22 and 23: Quality of life: no form performed.
Jerez Hospital	8	8/23/2021	The following protocol-mandated tests were not performed: Patient 735-4: Cycles 26, 27, 30: Patient Status: no ECOG performed. Cycle 30: Quality of life: form is not performed. Patient 735-1: Cycles 31, 33: Patient Status: ECOG is not performed. Cycle 31: Response assessment: sFLC-κ, sFLC-λ and sFLC ratio are not measured. Cycle 30: Quality of Life: the form is not performed.
Jerez Hospital	9	8/23/2021	In error, the following Patients were taking a 24mg dose of Dexamethasome when per protocol they were on a 20mg dose of Dexamethasome. Patient 735-4: Cycles 20-33 (22/04/2020 - 04/06/2021) Patient 735-1: Cycles 13-25 (07/10/2019 - 08/10/2020) By mistake, the Patients receive a 24mg dose instead of the 20mg dose stipulated by protocol. The physician continues to prescribe this dose for one year. During the monitoring visit on 08/20/2021, the CRA is informed of these facts. On 08/09/2021, the Study Coordinator and the Principal Investigator informed the CRA and agreed to correct the dose of the medication in the following cycles according to the protocol
Jerez Hospital	10	4-Oct-21	On September 14, Patient 738-01 from Jerez Hospital de la Frontera went for an afternoon check-up with the hematology service. After the consultation, the Patient and the family member accompanying her went to the pharmacy, at which time the pharmacist on duty, unfamiliar with the trial medication, was on duty. By mistake, Lenalidomide 10mg was dispensed from another trial (GEM2017FIT), whose manufacturer is CELGENE, lot 20F0833, expiration date 30/06/2022. The trial unit contacted Patient, who returned to the pharmacy on September 21, returned the medication from the other trial and the correct medication was dispensed. During that time period the Patient took 9 medicated capsules from the other trial. The physician had prescribed Lenalidomide 10mg; therefore the Patient took the correct mediation and dose. The Patient's safety was not compromised, nor is the primary endpoint of the study affected.

Jerez Hospital	11	4/9/2022	Patient 738-4: Cycles 35 and 37: Patient Status: no ECOG performed. Patient 738-1: Cycles 37 and 38: Patient's status (ECOG, Weight, ACR, Ecchymosis) is not reported in the medical record. Cycle 39: No visit was made. The date of the visit is noted and the fields in the Patient's status section are left blank. Cycle 39: Quality of Life Questionnaire was not completed.
Jerez Hospital	12	11-Jan-23	Patient 738-01: - Final visit: evaluation of the response: Bence-Jones protein is detected in 24h urine but due to Patient's low diuresis it is not quantified. - Cycle 41: the quality of life questionnaire is not performed.
Jerez Hospital	13	1/11/2023	Patient 738-4: - Cycle 38: Patient refers in this cycle that he had a confusion in taking medications, so he has taken dexamethasome 8mg daily for 6 days. - Cycles 37, 45: Response evaluation: No urine CM determined. - Cycles 37, 38, 40, 43, 44, 46: Patient Status: ECOG not determined. - Cycles 41, 46: Quality of life questionnaire is not performed.

CENTRE	DEVIATION NUMBER	DATE	DESCRIPTION
CHUAC	1	2/1/2019	The following protocol-mandated tests were not performed: Patient 739-1: - Cycle 2: response assessment. Urine CM at 24 h are not determined. - Cycle 3: Response evaluation. No 24 h urine MC determined.
CHUAC	2	11/21/2019	The following protocol-mandated tests were not performed: Patient 739-1: - Cycle 7 - Patient Status: ECOG. - Cycles 4 to 8 - Response Evaluation: 24h urine CM.
CHUAC	3	11/21/2019	Patient 739-2: The following tests required by protocol are not determined for this Patient: - Screening - Disease at diagnosis: CM in urine at 24h. - Selection - Baseline examination: ejection fraction (%). - Cycle 1 - Patient Status: Failure to determine if the hematological values on day 22 of treatment are correct due to laboratory error. - Cycles 5 and 8 - Patient Status: ECOG. - Cycles 3, 4, 5 and 8 - Response Assessment: 24h urine CM.
CHUAC	4	8/25/2020	Patient 739-2: The following tests required by protocol are not determined for this Patient: - Screening: Disease at diagnosis: ECOG. - Cycles 13, 14, 15, 16, 17 and 19 - Patient Status: ECOG. - Cycles 1 and 18 - Response Evaluation: 24-hour urine CM. - Cycles 13, 14, 16 and 17: Quality of Life Form.
CHUAC	5	7/21/2021	Patient 739-2: The following protocol-required tests are not determined for this Patient: Cycles 19, 22, 23, 26, 27, 28 and 29 - Patient Status: ECOG. Cycles 19 to 29 - Response evaluation: 24 hour urine CM.
CHUAC	6	4/20/2022	Patient 739-1: The following protocol-required tests are not determined for this Patient: Final visit and cycle 9 - Response assessment: serum free light chains
CHUAC	7	4/20/2022	Patient 739-2: The following protocol-required tests are not determined for this Patient: Cycles 30, 31 and 33 - Patient Status: ECOG. Cycle 29 - Response Evaluation: Serum Free Light Chains
CHUAC	8	9/27/2022	Patient 739-2: The following protocol-required tests are not determined for this Patient: - Final visit section final visit vital signs - Patient's status cycles 17, 22,23,26-29, 31-34, 36 ECOG - Cm urine cycles 31, 33, 34, 36 - Plasmacytoma

CHUAC	9	2/1/2019	Patient 739-1: The following tests required by protocol are not determined for this Patient: - Cycle 2: response assessment. The CM in urine at 24 h is not determined. - Cycle 3: response evaluation. Urine MC at 24 h are not determined.
CHUAC	10	11/21/2019	Patient 739-1: The following protocol-required tests are not determined for this Patient: - Cycle 7: Patient status: ECOG. - Cycles 4 to 8: response assessment: 24 h urine CM.
CHUAC	11	11/21/2019	Patient 739-2: The following protocol-required tests are not determined for this Patient: - Screening: disease at diagnosis: CM in urine at 24 h. - Selection: baseline examination: ejection fraction (%). - Cycle 1: Patient's condition: it is not determined whether the hematological values on day 22 of treatment are correct due to laboratory error. - Cycles 5 and 8: Patient status: ECOG. - Cycles 3, 4, 5 and 8: response assessment: 24 h urine CM.
CHUAC	12	8/25/2020	Patient 739-2: The following protocol-required tests are not determined for this Patient: - Screening: disease at diagnosis: ECOG. - Cycles 13, 14, 15, 16, 17 and 19: Patient status: ECOG. - Cycles 1 and 18: response assessment: 24 h urine CM. - Cycles 13, 14, 16 and 17: quality of life form.
CHUAC	13	7/21/2021	Patient 739-2: The following protocol-required tests are not determined for this Patient: - Cycles 19, 22, 23, 26, 27, 28 and 29: Patient status:ECOG. - Cycles 19 to 29: response assessment: CM urine at 24 h.
CHUAC	14	4/20/2022	Patient 739-2: The following protocol-required tests are not determined for this Patient: - Cycles 30, 31 and 33: Patient status: ECOG. - Cycle 29: response evaluation: serum free light chains.
CHUAC	15	4/20/2022	Patient 739-1: The following protocol-required tests are not determined for this Patient: - Final visit and cycle 9: response assessment: serum free light chains.