A Randomized, Open-Label, Controlled Phase 3 Study Comparing Daratumumab, Lenalidomide and Dexamethasone Induction followed by Linvoseltamab Versus continued Daratumumab, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

Estado	**Tipo de Participantes**	**Rangos de Edad**
Reclutando	No aportado	Mayores de 64 , Adultos (18-64 años)
Género	**Fases**	**Participantes esperados**
Ambos	Fase III	217
Resultados	**Bajo nivel intervención**	**Enfermedad rara**
Sin resultados	No	No
Cobertura geográfica	**Ámbitos del ensayo**	**Terapia avanzada**
Sin determinar	seguridad, eficacia, farmacocinética, farmacodinamica	NO

Información

Identificador
2024-519827-16-00 (CTIS)

Cod. Protocolo
EMN39

Área terapéutica
Enfermedades [C] - Cáncer [C04]|

Enfermedad investigada
Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

Título Científico
A Randomized, Open-Label, Controlled Phase 3 Study Comparing Daratumumab, Lenalidomide and

Dexamethasone Induction followed by Linvoseltamab Versus continued Daratumumab, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

Justificación

No aportado

Objetivo Principal

To compare the proportion of patients who achieve minimal residual disease (MRD) negative CR status as measured by clonoSEQ with a sensitivity of at least 10-5 between the two study arms

Variables de Evaluación Primaria

MRD negative CR status at 10-5 (as measured in BM by clonoSEQ assay) per IMWG criteria (S. Kumar et al., 2016) as determined by BICR
PFS per IMWG response criteria (S. Kumar et al., 2016) as determined by BICR, defined as the time from the date of randomization to the date of first documented evidence of progressive disease or death, whichever occurs first

Momentos temporales de evaluación primaria

No aportado

Objetivo Secundario

To compare OS between the two study arms

Variables de Evaluación Secundaria

The key secondary endpoint is overall survival (OS) from time of randomization.

Momentos temporales de evaluación secundaria

No aportado

Criterios de Inclusión

Participants must have confirmed diagnosis of symptomatic MM per IMWG criteria (Appendix 1). Provide informed consent signed by study patient. Able to understand and complete study-related questionnaires. Age 18 years (or

legal adult age in the country) or older at the time of informed consent. Participants must not be considered a candidate for high-dose chemotherapy (HDT) and ASCT due to: advanced age with or without comorbidities or for patients aged 18-69 the presence of significant comorbidities that are likely to have a negative impact on tolerability of HDT-ASCT The reason(s) for transplant ineligibility must be provided by the investigator. Participants must have measurable disease, as defined by at least 1 of the following (according to the 2016 IMWG response criteria): Serum monoclonal protein level 1 g/dL Quantitative immunoglobulin levels of 1 g/dL (Immunoglobulin A [IgA] and immunoglobulin D [IgD] myeloma only). Note: for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments (Visram et al., 2021). Urinary M-protein level of 200 mg over a 24-hour period Involved serum FLC level 10 mg/dL, along with an abnormal FLC ratio in patients with FLC only measurable myeloma NOTE: All attempts should be made to establish measurable disease at screening based on blood or urine central laboratory results. Under exceptional circumstances and with the sponsors approval, local laboratory results of blood, urine Mprotein measurements, and sFLC may be used to determine measurable disease if the results are 25% above the thresholds for measurability. Central laboratory results are still to be obtained prior to the start of administration of study treatment as a reference for response assessment. ECOG performance status of 0, 1, or 2. Participants must have clinical laboratory values meeting the below criteria. These laboratory values must be evaluated during screening and be re-evaluated within 72 hours prior to the first dose and the patient must meet all criteria at both assessments. If one or more criteria are not met 72 hours prior to dosing, 1 repeat of laboratory testing is permitted. ANC 1,000 cells/mm3 (1 x 109 cells/L) without growth factor support within 7 days for G-CSF and within 14 days for pegylated-G-CSF of the lab assessment. Hemoglobin 7.5 g/dL (4.65 mmol/L) without red blood cell transfusions within 7 days of the lab assessment. Platelet counts of 75,000 cells/mm3 for participants who have bone marrow plasmacytosis of <50%, or 50,000 cells/mm3 for participants who have bone marrow plasmacytosis of 50%. A participant may not have received a platelet transfusion or thrombopoietin receptor agonist within 7 days of the lab assessment. Serum creatinine clearance by MDRD (Modification of Diet in Renal Disease) 30 mL/min. A participant with a creatinine clearance by MDRD who does not meet eligibility criteria may be considered for enrollment if a measured creatinine clearance, based on 24-hour urine collection or another reliable method is 30 mL/min. Total bilirubin 2 times the institutional upper limit of the normal values (IULN), with the exception of participants that have known or suspected Gilberts syndrome, (in which case direct bilirubin 2.0 x ULN is required). Total AST and ALT 3 X ULN. Serum calcium corrected for albumin 14 mg/dL (3.5 mmol/L) or free ionized calcium 6.5 mg/dL (1.6 mmol/L). Be willing and able to comply with clinic visits and study-related procedures, including serial bone marrow evaluations. Be willing to be hospitalized or remain in close proximity (within 30 minutes) to the hospital at minimum after step-up dose 1 if randomized to the experimental arm. Due to the embryo-fetal risk associated with IMiDs, all participants must adhere to the global PPP or local PPP/REMS program for lenalidomide.

Criterios de Exclusión

IMWG Frailty Index of 2 (i.e. frail patients) with the exception of participants who have a score of 2 and are frail based on age alone (Palumbo et al., 2015). Participants who have a frailty score of 2 based on age alone will be capped at 10% of the total study population. History of severe allergic reaction attributed to any study drug or excipient (ie, monoclonal antibodies and/or their excipients) used to treat indications other than MM. A severe allergic reaction is defined for this purpose as requiring hospitalization and/or treatment with epinephrine. Prior infusion reactions with monoclonal antibody-based therapeutics will not be considered evidence of an allergic reaction. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information. Known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of lenalidomide (eg, gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of lenalidomide via nasogastric tube or gastrostomy tube is not allowed. Participants who required plasmapheresis within 4 weeks from C1D1. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or another uncontrolled infection (such as cytomegalovirus [CMV]). Additional guidelines for HIV, HBV, and HCV are: Participants with HIV, without history of AIDS defining condition, who have controlled infection (undetectable viral load and CD4 count above 350 cells/L on a stable antiviral regimen and have not changed anti-retroviral treatment within 6 months prior to treatment initiation) are permitted. Participants with HBV: defined by a positive test HBsAg (seropositive for hepatitis B). Participants with resolved infection (ie, participants who are HBsAg negative with antibodies to total anti-HBc with or without the presence of anti-HBs) must be screened using RT-PCR measurement of HBV-DNA levels. Those who are RT-PCR positive will be excluded (see also screening guide

hepatitis B, Appendix 3). Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV-DNA by RTPCR. Participants who are HCV antibody positive who have controlled infection (undetectable HCV RNA by PCR, either spontaneously or in response to a successful prior course of anti- HCV therapy at least 12 weeks prior to treatment initiation) are permitted. Participants will be excluded if they have any of the following malignancies: Myelodysplastic syndrome or B cell malignancy (other than multiple myeloma) Any history of malignancy that is considered at high risk of recurrence requiring systemic therapy, other than multiple myeloma, Prior or concurrent malignancy within 24 months prior to the date of randomization (other than multiple myeloma) The only allowed exceptions are malignancies adequately treated within the last 24 months that are considered cured: Non-muscle invasive bladder cancer (solitary Ta-papillary urothelial neoplasm of low malignancy or low grade, <3 cm, no carcinoma in situ) Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone Noninvasive cervical cancer Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history of localized breast cancer (anti-hormonal therapy is permitted) Localized prostate cancer (M0, N0) with a Gleason Score 7a, treated locally only (radical prostatectomy/radiation therapy/focal treatment) Other malignancy that is considered cured with minimal risk of recurrence are permitted following consultation with and approval by the sponsors medical monitor. Investigational, live or live attenuated, or replication-competent viral vector vaccine within 28 days prior to first study treatment. History of allogeneic hematopoietic stem cell transplantation or solid organ transplant at any time. Known hypersensitivity to both allopurinol and rasburicase. Unable or unwilling to undergo antithrombotic prophylactic treatment as determined by investigator. Participants who defer transplant due to personal preference (who would otherwise be candidates for transplant based on age and absence of comorbid conditions that would preclude transplant candidacy). Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor. Pregnant or breastfeeding females. Females of childbearing potential (FOCBP)* or sexually active males who are unwilling to practice highly effective contraception prior C1D1, during the study, and for at least 6 months after the last dose. For males, sperm donation is prohibited during the study and for at least 6 months after the last dose of any study drug. Highly effective contraceptive measures include: stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion/ligation; vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the FOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or sexual abstinence, . Pregnancy testing and contraception are required for FOCBP. Pregnancy testing and contraception are not required for females who are post-menopausal or permanently sterile. FOCBP must agree to not donate eggs (ova, oocytes) for the purpose of assisted reproduction during the study and for at least 6 months after the last dose of any study drug. *FOCBP are defined as females who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Screen Failures Participants who fail to meet the inclusion and exclusion criteria may be rescreened only once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are eligible for rescreening must sign a new ICF and will then be assigned a new screening number. Participants with non-secretory MM, active plasma cell leukemia defined as either having 5% of peripheral white blood cells comprised of CD138+ plasma cells, known light-chain (AL) amyloidosis in the presence of a concurrent diagnosis of myeloma, any other form of amyloidosis, Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). Any prior therapy for monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or MM, with the exception of: Focal Radiation, such as on an emergency basis for a presentation with spinal cord compression, or on a palliative basis to improve pain control. A washout period of at least 2 weeks for radiation therapy should be met prior C1D1. Radiotherapy within 14 days of C1D1 on measurable soft tissue plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management. A short course of corticosteroids for emergency use (maximum dexamethasone equivalent 40mg/day for 4 days) will be allowed up to 5 days prior to C1D1, provided that the participant remains eligible based on the measurable disease criteria defined above (see Appendix 2). Participants who have received or are receiving any investigational agent or cell therapy with known or suspected activity against MM (or another plasma cell disorder), or those whose AEs due to agents administered earlier (such as radiation and/or corticosteroids) have not recovered to a severity of grade 0 or grade 1. Participants who have undergone any major surgery within 4 weeks prior to C1D1, with the following exceptions: Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to C1D1. Planned elective minor surgery

unrelated to the participants diagnosis of myeloma, such as hernia repair, may be allowed, at the discretion of the Principal Investigators and Study Sponsor, as long as it was performed at least 2 weeks prior to C1D1, and participants have fully recovered from this procedure. Participants who have known central nervous system (CNS) or meningeal involvement with MM or known or suspected progressive multifocal leukoencephalopathy (PML), a history of a neurocognitive condition or CNS movement disorder, OR a history of seizure, transient ischemic attack (TIA), stroke or seizure within 12 months prior to study C1D1. Participants who have uncontrolled intercurrent illness including, but not limited to: ongoing or active viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy Active autoimmune disease or a documented history of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing symptomatic congestive heart failure (for example, NYHA Class III or IV Heart Failure; New York Heart Association (NYHA) Classification, 2018) cardiac dysfunction evidenced by ejection fraction <40% by echocardiogram or multigated acquisition scan (Bingham & Hachamovitch, 2008) angina pectoris hypertension (defined as an average systolic blood pressure >159 mm Hg or diastolic >99 mm Hg, despite optimal treatment) cardiac arrhythmia (except clinically insignificant, asymptomatic bradycardia) Has COPD with an FEV1 <50% of predicted. (FEV1 testing is required for participants suspected of having COPD). asthma (moderate or severe persistent asthma within the past 2 years, or current uncontrolled asthma of any classification) diabetes (HbA1C averaging >8% in the 6 months prior to C1D1) psychiatric condition or diagnosis (alcohol or drug abuse, severe dementia, or altered mental status), or social situations that would limit compliance with study requirements, in the opinion of the investigators or Sponsor. History of myocardial infarction within the previous 12 months prior to C1D1.

Calendario

(Última actualización: 22/07/2026)

Autorización	Inicio de Ensayo	Inclusión Primer Paciente	Interrumpido	Reiniciado
04/09/2025	21/10/2025	22/12/2025	No aportado	No aportado

Fin de reclutamiento	Fin prematuro (España)	Fin prematuro (Global)	Fin del ensayo en España	Fin del ensayo global
No aportado	No aportado	No aportado	No aportado	No aportado

Promotor

European Myeloma Network B.V. Netherlands

Blaak 555

Contact Person

Pieter Sonneveld

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Monetary support: N/A

Tipo de promotor: Comercial

Ceim

CEIm Hospital Universitari de Bellvitge

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presidenciaceic@bellvitgehospital.cat

Centros

Activo (14/10/2025)

Hospital Clinic De Barcelona

Barcelona

BARCELONA

724001; Hematología

Activo (18/09/2025)

Hospital Universitario Marques De Valdecilla

Santander

CANTABRIA

724003; Hematología

Activo (07/10/2025)

Hospital Universitario Y Politecnico La Fe

Valencia

VALENCIA

724004; Hematología y Hemoterapia

Activo (07/10/2025)

Hospital Universitario 12 De Octubre

Madrid

MADRID

724005; Hematología y Hemoterapia

Activo (05/11/2025)

Institut Catala D´oncologia

Badalona

BARCELONA

724002; Hematología

Medicamentos

Revlimid 15 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid AL 5 mg Hartkapseln
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid AL 25 mg Hartkapseln
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid AL 15 mg Hartkapseln
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

LYNOZYFIC 200 mg concentrate for solution for infusion
SOLUTION FOR INFUSION
SOLUTION FOR INFUSION

-
Principios Activos: N/A

Experimental

Lenalidomide Accord 10 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

LYNOZYFIC 5 mg concentrate for solution for infusion
SOLUTION FOR INFUSION
SOLUTION FOR INFUSION

-
Principios Activos: N/A

Experimental

Revlimid 5 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

DARZALEX 1800 mg solution for injection
SOLUTION FOR INJECTION
SUBCONJUNCTIVAL USE

Código ATC: L01FC01 - DARATUMUMAB
Principios Activos: N/A

Huérfano Experimental

Lenalidomid AL 10 mg Hartkapseln
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid STADA 10 mg Hartkapseln
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Dexamethason CF 20 mg/ml, injectievloeistof
SOLUTION FOR INJECTION
ORAL USE

Código ATC: H02AB02 - DEXAMETASONA
Principios Activos: N/A

Experimental

Lenalidomide Accord 25 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomide Accord 5 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Revlimid 10 mg hard capsules
CAPSULE, HARD
ORAL USE

Revlimid 25 mg hard capsules
CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid STADA 5 mg Hartkapseln

CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid STADA 15 mg Hartkapseln

CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Dexamethason Teva 4 mg, tabletten

TABLET
ORAL USE

Código ATC: H02AB02 - DEXAMETASONA
Principios Activos: N/A

Experimental

Lenalidomide Accord 15 mg hard capsules

CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Lenalidomid STADA 25 mg Hartkapseln

CAPSULE, HARD
ORAL USE

Código ATC: L04AX04 - LENALIDOMIDA
Principios Activos: N/A

Experimental

Sin resultados

A Randomized, Open-Label, Controlled Phase 3 Study Comparing Daratumumab, Lenalidomide and Dexamethasone Induction followed by Linvoseltamab Versus continued Daratumumab, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

State	Type of participants	Age Ranges
Recruiting	Not provided	Older than 64 , Adults (18-64 years)
Gender	**Phases**	**Expected Participants**
Both	Phase III	217
Results	**Low level of intervention**	**Rare disease**
No results	No	No
Geographic coverage	**Areas of the study**	**Advanced therapy**
Undetermined	safety, effectiveness, pharmacokinetics, pharmacodynamics	NO

Information

Identifier
2024-519827-16-00 (CTIS)

Protocol Code
EMN39

Therapeutic area
Diseases [C] - Cancer [C04]|

Investigated Disease
Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

Scientific Title
A Randomized, Open-Label, Controlled Phase 3 Study Comparing Daratumumab, Lenalidomide and

Dexamethasone Induction followed by Linvoseltamab Versus continued Daratumumab, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients

Rationale

Not provided

Main Objective

To compare the proportion of patients who achieve minimal residual disease (MRD) negative CR status as measured by clonoSEQ with a sensitivity of at least 10-5 between the two study arms

Primary Endpoints

MRD negative CR status at 10-5 (as measured in BM by clonoSEQ assay) per IMWG criteria (S. Kumar et al., 2016) as determined by BICR
PFS per IMWG response criteria (S. Kumar et al., 2016) as determined by BICR, defined as the time from the date of randomization to the date of first documented evidence of progressive disease or death, whichever occurs first

Temporary moments of secondary assessment

Not provided

Secondary Objective

To compare OS between the two study arms

Secondary Endpoints

The key secondary endpoint is overall survival (OS) from time of randomization.

Temporary moments of secondary assessment

Not provided

Inclusion criteria

Participants must have confirmed diagnosis of symptomatic MM per IMWG criteria (Appendix 1). Provide informed consent signed by study patient. Able to understand and complete study-related questionnaires. Age 18 years (or

legal adult age in the country) or older at the time of informed consent. Participants must not be considered a candidate for high-dose chemotherapy (HDT) and ASCT due to: advanced age with or without comorbidities or for patients aged 18-69 the presence of significant comorbidities that are likely to have a negative impact on tolerability of HDT-ASCT The reason(s) for transplant ineligibility must be provided by the investigator. Participants must have measurable disease, as defined by at least 1 of the following (according to the 2016 IMWG response criteria): Serum monoclonal protein level 1 g/dL Quantitative immunoglobulin levels of 1 g/dL (Immunoglobulin A [IgA] and immunoglobulin D [IgD] myeloma only). Note: for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments (Visram et al., 2021). Urinary M-protein level of 200 mg over a 24-hour period Involved serum FLC level 10 mg/dL, along with an abnormal FLC ratio in patients with FLC only measurable myeloma NOTE: All attempts should be made to establish measurable disease at screening based on blood or urine central laboratory results. Under exceptional circumstances and with the sponsors approval, local laboratory results of blood, urine Mprotein measurements, and sFLC may be used to determine measurable disease if the results are 25% above the thresholds for measurability. Central laboratory results are still to be obtained prior to the start of administration of study treatment as a reference for response assessment. ECOG performance status of 0, 1, or 2. Participants must have clinical laboratory values meeting the below criteria. These laboratory values must be evaluated during screening and be re-evaluated within 72 hours prior to the first dose and the patient must meet all criteria at both assessments. If one or more criteria are not met 72 hours prior to dosing, 1 repeat of laboratory testing is permitted. ANC 1,000 cells/mm3 (1 x 109 cells/L) without growth factor support within 7 days for G-CSF and within 14 days for pegylated-G-CSF of the lab assessment. Hemoglobin 7.5 g/dL (4.65 mmol/L) without red blood cell transfusions within 7 days of the lab assessment. Platelet counts of 75,000 cells/mm3 for participants who have bone marrow plasmacytosis of <50%, or 50,000 cells/mm3 for participants who have bone marrow plasmacytosis of 50%. A participant may not have received a platelet transfusion or thrombopoietin receptor agonist within 7 days of the lab assessment. Serum creatinine clearance by MDRD (Modification of Diet in Renal Disease) 30 mL/min. A participant with a creatinine clearance by MDRD who does not meet eligibility criteria may be considered for enrollment if a measured creatinine clearance, based on 24-hour urine collection or another reliable method is 30 mL/min. Total bilirubin 2 times the institutional upper limit of the normal values (IULN), with the exception of participants that have known or suspected Gilberts syndrome, (in which case direct bilirubin 2.0 x ULN is required). Total AST and ALT 3 X ULN. Serum calcium corrected for albumin 14 mg/dL (3.5 mmol/L) or free ionized calcium 6.5 mg/dL (1.6 mmol/L). Be willing and able to comply with clinic visits and study-related procedures, including serial bone marrow evaluations. Be willing to be hospitalized or remain in close proximity (within 30 minutes) to the hospital at minimum after step-up dose 1 if randomized to the experimental arm. Due to the embryo-fetal risk associated with IMiDs, all participants must adhere to the global PPP or local PPP/REMS program for lenalidomide.

Exclusion criteria

IMWG Frailty Index of 2 (i.e. frail patients) with the exception of participants who have a score of 2 and are frail based on age alone (Palumbo et al., 2015). Participants who have a frailty score of 2 based on age alone will be capped at 10% of the total study population. History of severe allergic reaction attributed to any study drug or excipient (ie, monoclonal antibodies and/or their excipients) used to treat indications other than MM. A severe allergic reaction is defined for this purpose as requiring hospitalization and/or treatment with epinephrine. Prior infusion reactions with monoclonal antibody-based therapeutics will not be considered evidence of an allergic reaction. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information. Known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of lenalidomide (eg, gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of lenalidomide via nasogastric tube or gastrostomy tube is not allowed. Participants who required plasmapheresis within 4 weeks from C1D1. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or another uncontrolled infection (such as cytomegalovirus [CMV]). Additional guidelines for HIV, HBV, and HCV are: Participants with HIV, without history of AIDS defining condition, who have controlled infection (undetectable viral load and CD4 count above 350 cells/L on a stable antiviral regimen and have not changed anti-retroviral treatment within 6 months prior to treatment initiation) are permitted. Participants with HBV: defined by a positive test HBsAg (seropositive for hepatitis B). Participants with resolved infection (ie, participants who are HBsAg negative with antibodies to total anti-HBc with or without the presence of anti-HBs) must be screened using RT-PCR measurement of HBV-DNA levels. Those who are RT-PCR positive will be excluded (see also screening guide

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Investigational, live or live attenuated, or replication-competent viral vector vaccine within 28 days prior to first study treatment. History of allogeneic hematopoietic stem cell transplantation or solid organ transplant at any time. Known hypersensitivity to both allopurinol and rasburicase. Unable or unwilling to undergo antithrombotic prophylactic treatment as determined by investigator. Participants who defer transplant due to personal preference (who would otherwise be candidates for transplant based on age and absence of comorbid conditions that would preclude transplant candidacy). Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor. Pregnant or breastfeeding females. Females of childbearing potential (FOCBP)* or sexually active males who are unwilling to practice highly effective contraception prior C1D1, during the study, and for at least 6 months after the last dose. For males, sperm donation is prohibited during the study and for at least 6 months after the last dose of any study drug. Highly effective contraceptive measures include: stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion/ligation; vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the FOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or sexual abstinence, . Pregnancy testing and contraception are required for FOCBP. Pregnancy testing and contraception are not required for females who are post-menopausal or permanently sterile. FOCBP must agree to not donate eggs (ova, oocytes) for the purpose of assisted reproduction during the study and for at least 6 months after the last dose of any study drug. *FOCBP are defined as females who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Screen Failures Participants who fail to meet the inclusion and exclusion criteria may be rescreened only once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are eligible for rescreening must sign a new ICF and will then be assigned a new screening number. Participants with non-secretory MM, active plasma cell leukemia defined as either having 5% of peripheral white blood cells comprised of CD138+ plasma cells, known light-chain (AL) amyloidosis in the presence of a concurrent diagnosis of myeloma, any other form of amyloidosis, Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). Any prior therapy for monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or MM, with the exception of: Focal Radiation, such as on an emergency basis for a presentation with spinal cord compression, or on a palliative basis to improve pain control. A washout period of at least 2 weeks for radiation therapy should be met prior C1D1. Radiotherapy within 14 days of C1D1 on measurable soft tissue plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management. A short course of corticosteroids for emergency use (maximum dexamethasone equivalent 40mg/day for 4 days) will be allowed up to 5 days prior to C1D1, provided that the participant remains eligible based on the measurable disease criteria defined above (see Appendix 2). Participants who have received or are receiving any investigational agent or cell therapy with known or suspected activity against MM (or another plasma cell disorder), or those whose AEs due to agents administered earlier (such as radiation and/or corticosteroids) have not recovered to a severity of grade 0 or grade 1. Participants who have undergone any major surgery within 4 weeks prior to C1D1, with the following exceptions: Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to C1D1. Planned elective minor surgery

unrelated to the participants diagnosis of myeloma, such as hernia repair, may be allowed, at the discretion of the Principal Investigators and Study Sponsor, as long as it was performed at least 2 weeks prior to C1D1, and participants have fully recovered from this procedure. Participants who have known central nervous system (CNS) or meningeal involvement with MM or known or suspected progressive multifocal leukoencephalopathy (PML), a history of a neurocognitive condition or CNS movement disorder, OR a history of seizure, transient ischemic attack (TIA), stroke or seizure within 12 months prior to study C1D1. Participants who have uncontrolled intercurrent illness including, but not limited to: ongoing or active viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy Active autoimmune disease or a documented history of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing symptomatic congestive heart failure (for example, NYHA Class III or IV Heart Failure; New York Heart Association (NYHA) Classification, 2018) cardiac dysfunction evidenced by ejection fraction <40% by echocardiogram or multigated acquisition scan (Bingham & Hachamovitch, 2008) angina pectoris hypertension (defined as an average systolic blood pressure >159 mm Hg or diastolic >99 mm Hg, despite optimal treatment) cardiac arrhythmia (except clinically insignificant, asymptomatic bradycardia) Has COPD with an FEV1 <50% of predicted. (FEV1 testing is required for participants suspected of having COPD). asthma (moderate or severe persistent asthma within the past 2 years, or current uncontrolled asthma of any classification) diabetes (HbA1C averaging >8% in the 6 months prior to C1D1) psychiatric condition or diagnosis (alcohol or drug abuse, severe dementia, or altered mental status), or social situations that would limit compliance with study requirements, in the opinion of the investigators or Sponsor. History of myocardial infarction within the previous 12 months prior to C1D1.

Calendar

(Last Update: 22/07/2026)

Authorization	Start of Trial	First patient inclusion	Halted	Restarted
04/09/2025	21/10/2025	22/12/2025	Not aported	Not aported

End of recruitment	Premature end (Spain)	Premature End (Global)	Trial end (Spain)	Trial end (Global)
Not aported	Not aported	Not aported	Not aported	Not aported

Sponsor

European Myeloma Network B.V. Netherlands

Blaak 555

Contact Person

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Monetary support: N/A

Sponsor type: Commercial

Ceim

CEIm Hospital Universitari de Bellvitge

Feixa Llarga, s/n - Antiguo Módulo Banco de Santander 08907 Hospitalet de Llobregat

presidenciaceic@bellvitgehospital.cat

Sites

Active (14/10/2025)

Hospital Clinic De Barcelona

Barcelona

BARCELONA

724001; Hematología

Active (18/09/2025)

Hospital Universitario Marques De Valdecilla

Santander

CANTABRIA

724003; Hematología

Active (07/10/2025)

Hospital Universitario Y Politecnico La Fe

Valencia

VALENCIA

724004; Hematología y Hemoterapia

Active (07/10/2025)

Hospital Universitario 12 De Octubre

Madrid

MADRID

724005; Hematología y Hemoterapia

Active (05/11/2025)

Institut Catala D´oncologia

Badalona

BARCELONA

724002; Hematología

Medication

Revlimid 15 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid AL 5 mg Hartkapseln
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid AL 25 mg Hartkapseln
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid AL 15 mg Hartkapseln
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

LYNOZYFIC 200 mg concentrate for solution for infusion
SOLUTION FOR INFUSION
SOLUTION FOR INFUSION

-
Active Principles: N/A

Experimental

Lenalidomide Accord 10 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

LYNOZYFIC 5 mg concentrate for solution for infusion
SOLUTION FOR INFUSION
SOLUTION FOR INFUSION

-
Active Principles: N/A

Experimental

Revlimid 5 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

DARZALEX 1800 mg solution for injection
SOLUTION FOR INJECTION
SUBCONJUNCTIVAL USE

ATC code: L01FC01 - DARATUMUMAB
Active Principles: N/A

Orphan Experimental

Lenalidomid AL 10 mg Hartkapseln
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid STADA 10 mg Hartkapseln
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Dexamethason CF 20 mg/ml, injectievloeistof
SOLUTION FOR INJECTION
ORAL USE

ATC code: H02AB02 - DEXAMETASONA
Active Principles: N/A

Experimental

Lenalidomide Accord 25 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomide Accord 5 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Revlimid 10 mg hard capsules
CAPSULE, HARD
ORAL USE

Revlimid 25 mg hard capsules
CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid STADA 5 mg Hartkapseln

CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid STADA 15 mg Hartkapseln

CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Dexamethason Teva 4 mg, tabletten

TABLET
ORAL USE

ATC code: H02AB02 - DEXAMETASONA
Active Principles: N/A

Experimental

Lenalidomide Accord 15 mg hard capsules

CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

Lenalidomid STADA 25 mg Hartkapseln

CAPSULE, HARD
ORAL USE

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

No results