PRIMARY PLASMA CELL LEUKEMIA: A PROSPECTIVE PHASE II STUDY INCORPORATING DARATUMUMAB TO CHEMOTHERAPY AND STEM CELL TRANSPLANTATION

PCL-2 STUDY

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.0 dated 06/06/2024

Project Code: APHP190205 / EUDRACT no: 2019-004170-26 /EU CT N° 2024-515037-15-00

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SIGNATURE page for a research PROTOCOL

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Title: **PRIMARY PLASMA CELL LEUKEMIA: A PROSPECTIVE PHASE II STUDY INCORPORATING DARATUMUMAB TO CHEMOTHERAPY AND STEM CELL TRANSPLANTATION**

Version 4.0 dated 06/06/2024

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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2 LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Sécurité des Médicaments et des Produits de santé
ALT	Alanine aminotransferase
ANC	absolute neutrophil count
AST	and aspartate aminotransferase
ASCT	autologous stem cell transplantation
CBC	Complete Blood Count
CCTAE	common toxicity criteria
CPP	Comité de Protection des Personnes
CR	Complete Response
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
GI	Gastro intestinal
IMWG	International Myeloma Working Group
ISS	International Staging System
VRD	Bortezomib-Lenalidomide-Dexamethasone
MHSC	Mobilization and harvesting stem cells
MM	multiple myeloma
MRD	minimal-residual disease
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
ORR	Overall response rate
OS	Overall survival
PBSC	Peripheral Blood Hematopoietic Stem Cells
PCL	primitive plasma cell leukemia
PFS	progression-free survival
SAE	Serious Adverse Event
SC	Subcutaneous
SPM	Second primary malignancy
TEAE	Treatment Emergent Adverse Event
TTP	Time to progression
ULN	upper limit of the normal range
VGPR	Very Good Partial Response

3 SUMMARY

Full title	PRIMARY PLASMA CELL LEUKEMIA: A PROSPECTIVE PHASE II STUDY INCORPORATING DARATUMUMAB TO CHEMOTHERAPY AND STEM CELL TRANSPLANTATION
Acronym/reference	PCL-2
Coordinating investigator	Bruno Royer Immuno-Hematology Unit, St Louis Hospital, Paris
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Primary plasma cell leukemia (pPCL) is a rare form of plasma cell malignancy (2-4% of multiple myeloma) with poor prognosis (overall survival (OS) < 12 months with conventional chemotherapy). Bortezomib-based regimens have shown promising results in small retrospective studies, and transplantation (auto and/or allograft) may improve OS for selected young patients. The IFM group recently published a prospective study in 40 pPCL patients, with alternate Bortezomib-Dexamethasone-Doxorubicin/Cyclophosphamide (PAD/VCD) as induction before high dose Melphalan plus autologous stem cell transplantation (HDM/ASCT), followed by reduced intensity conditioning-allograft (RIC-Allo) or second HDM/ASCT plus consolidation/maintenance with Bortezomib-Lenalidomide-Dexamethasone/Lenalidomide. Overall, 27 patients (69%) were responder to induction and 35% achieved VGPR or better; one patient underwent a syngeneic allograft and 25 HDM/ASCT: 16 of them subsequently received a RIC-allograft, 7 a second transplant followed by consolidation/maintenance. The median PFS and OS were 15 and 36 months, respectively. OS seems to be superior in the double transplant/maintenance group compared to the allotransplant group on landmark analysis. The Italian group also recently reported a prospective trial in pPCL involving 23 patients treated with lenalidomide-dexamethasone: overall the median PFS and OS were 14 and 28 months, respectively. Nine of 15 patients eligible for transplant could receive HDM/ASCT after induction and PFS and OS were 27 months and not reached, respectively. Daratumumab, a monoclonal antibody against CD38 that is highly expressed by plasma cells, is highly effective in relapsed/refractory patients with multiple myeloma (MM), alone and in combination with Lenalidomide. The combination Daratumumab and Bortezomib-Lenalidomide-Dexamethasone (Dara-VRD) has been recently tested for newly diagnosed multiple myeloma patients with

	impressive results and acceptable tolerability. The subcutaneous formulation of Daratumumab have also been tested in this context with no new safety concerns. With the aim to improve hematological responses and survival in pPCL patients, we propose to combine Daratumumab SC and Bortezomib-Lenalidomide-Dex (Dara-VRD) as induction, followed by double HDM/ASCT and prolonged consolidation of 2 years (with Dara-VRD for 1 year then Lenalidomide for 1 year).
Main objective and primary endpoint	**The primary objective** is to determine the best overall Response rate at completion of induction phase (very good partial response or better) **The primary endpoint** is the VGPR or better rate at the completion of induction phase (according to the IMWG response criteria)
Secondary objectives and endpoints	**The main secondary objective** is to evaluate progression-free survival **The other secondary objectives** are: - to assess overall hematological response rates - to evaluate overall survival - to assess safety and toxicity according to NCI CTCAE - to assess cytogenetic abnormalities of tumoral plasma cell - to analyze the prognostic value of minimal-residual disease (MRD) by sequencing (NGS), after completion of induction, before second consolidation, before Len consolidation and at the end of treatment. - to evaluate quality of life (EORTC QLQ-C30 domain scores) **The secondary endpoints** are: - Progression-free Survival, Overall Survival, Time to progression and Duration of Response. - overall hematological response rates - Assess safety by type, frequency, severity, relationship of adverse events to study treatment and changes in vital signs, physical exams. Incidence of Treatment Emergent Adverse Event (TEAE), Serious Adverse Event (SAE) and laboratory abnormalities using National Cancer Institute (NCI) common toxicity criteria (CCTAE V4). - Evaluate response according to chromosomal structural abnormalities such as del(17p), t(4;14), t(11;14), t(14;16), t(14;20), amp(1q) and del(1p). - Minimal residual disease (MRD) assessed by NGS - Quality of life (EORTC QLQ-C30 domain scores)
Design of the study	**Induction phase**

After inclusion in the trial, patients will receive 4 days of dexamethasone. According to local practice, one dose of doxorubicine (30 mg/m2 IV) or cyclophosphamide (750 mg/m2 IV) may also be added to reduce the tumoral mass and minimize the risk of tumor lysis syndrome (TLS).

I. Induction Treatment (4 months): Subject will receive 4 x 28 days cycles of Dara-VRD induction therapy as described below:

agent	dose/day	route	cycle	days
Daratumumab	1800 mg	s.c	1,2,3,4	1, 8, 15, 22 (cycle 1 and 2) 1 15 (cycle 3 and 4)
Bortezomib	1.3 mg/m²	s.c	1, 2, 3, 4	1, 4, 8, 11
Lenalidomide*	25 mg†	p.o	1, 2, 3, 4	From D1 to D21 of each cycle
Dexamethasone	20 mg	p.o/ iv	1,2, 3, 4	1,2,8,9,15,16,22, 23

*: The start dose of lenalidomide will be reduced depending on renal function. Patients with impaired renal function (calculated or measured creatinine clearance < 50 mL/minute) will have lenalidomide dose reduction otherwise they will receive full dose lenalidomide (25mg).

Tumor-lysis prophylaxis and monitoring is required during induction treatment (according to local practice).

II. Disease assessment (local assessment) will be performed at the end of the induction to determine if patient continue with the study or not
- Responding patients (response ≥ SD and circulating plasma cell < 1 %) => pursuit of the study
- Non-responding patient (response < SD or circulating plasma cell ≥ 1 %) => off study

Mobilization and Harvesting Stem Cells

Stem cell mobilization will be performed using cyclophosphamide (recommended dose of 3 g/m2) after Cycle 4 and stem cells will be harvested based on response to mobilization. The use of GCSF and Plerixafor are permitted per institutional practice: sufficient stem cells should be harvested to enable two transplants (≥ 5.10^6 CD34/kg).

High Dose Melphalan/ASCT n°1

	All eligible patients will start intensification with High Dose Melphalan between 2 and 4 weeks after stem cell collection. - Mephalan 200mg/m2 as conditioning therapy. For patients with a creatinine clearance < 30 ml/min, Melphalan dose should be reduced to 140 mg/m². - Stem cell reinfusion: subjects will have a single re-infusion of stem cells (minimum $2.5.10^6$ CD34/kg) 24-48 hours after high-dose melphalan (+ permitted tolerance). - Engraftment/Recovery (Day 1-60 post ASCT) Subjects will be monitored for successful engraftment; support therapy will be administered according to institutional/study group standards **First consolidation (60 days)** Consolidation therapy start at time of complete hematological recovery and according to the investigator's opinion (subject fit enough to tolerate subsequent systemic therapy: within 2 months after ASCT). Subjects will receive a further 2 x 28-day cycles of Dara-VRD: - Daratumumab 1800 mg s.c D1 D15 - Bortezomib 1.3 mg/m2 s.c D1 D8 D15 D22 - Lenalidomide 25 mg p.o from D1 to D21 - Dexa 20 mg p.o/iv D1 D8 D15 D22 **High Dose Melphalan/ASCT n°2** - Subjects will receive melphalan 200mg/m² as conditioning therapy. For patients with a creatinine clearance < 30 ml/min, Melphalan dose should be reduced to 140 mg/m². - Stem cell reinfusion: subjects will have a single re-infusion of stem cells (minimum $2.5.10^6$ CD34/kg) 24-48 hours after high-dose melphalan (+ permitted tolerance) - Engraftment/Recovery (Day 1-60 post ASCT) **Second consolidation phase (2 years)** Consolidation therapy start at time of complete hematological recovery and according to the investigator's opinion (subject fit enough to tolerate subsequent systemic therapy: within 2 months after ASCT). This phase will be conducted according to two steps: - <u>Consolidation 1 (1 year)</u>: Patients will receive Dara-VRD every 2 months for 6 cycles: o Daratumumab 1800 mg s.c D1 o Bortezomib 1.3 mg/m2 s.c D1 D8 D15 D22 o Lenalidomide 25 mg p.o from D1 to D21 o Dexamethasone 20 mg p.o/iv D1 D8 D15 D22

	- Consolidation 2 (1 year): Patient will receive Lenalidomide every 28 days ○ Lenalidomide 25 mg from D1 to D21 / 28 days *Note.* During all treatment period, Lenalidomide dose will be readjusted according to patient's renal function status. The dose adaptation will follow usual recommendations.
Category	Cat. 2
Population of study participants	**Screening and Eligibility** The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility that must take place within 21 days prior to initiation of therapy. The patients must meet the eligibility criteria below to enter the study.

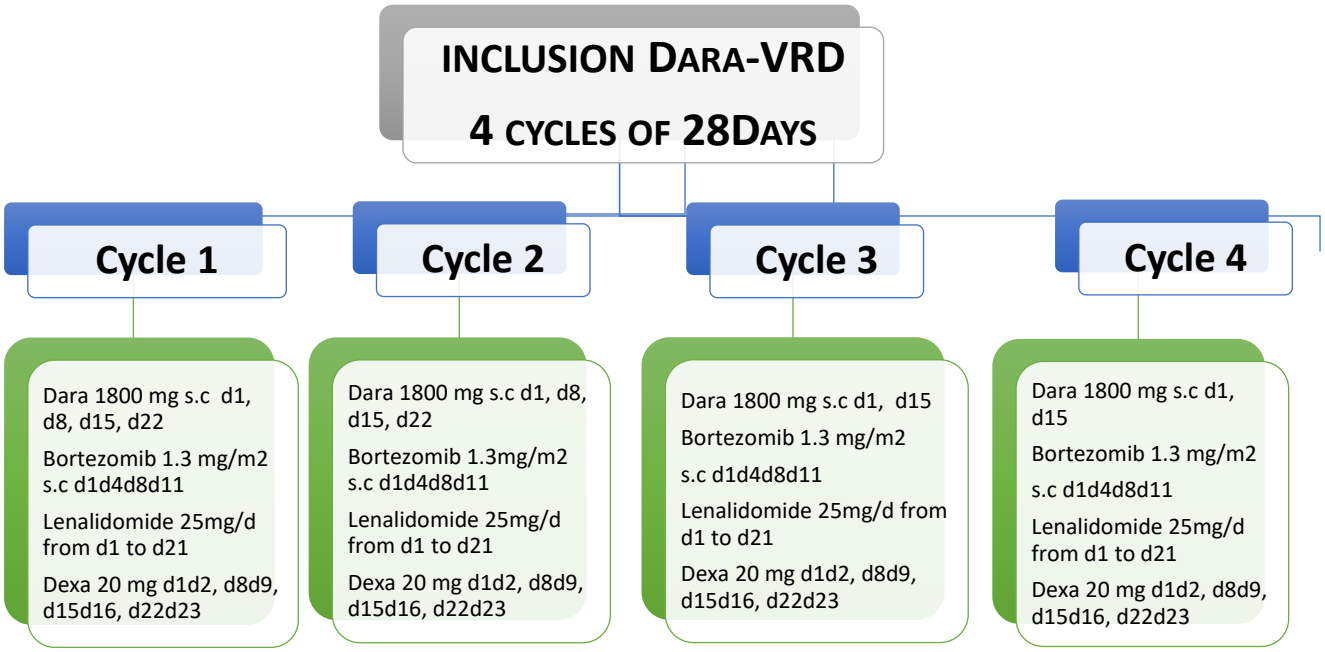
Inclusion criteria	1. Male or female patients 18 to 69 years old.
	2. Patient with primary plasma cell leukemia disease as defined by the recent International Myeloma Working Group (IMWG 2021): ≥ 5% circulating plasma cells in peripheral blood smears
	3. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care
	4. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
	5. Eligible for high dose Melphalan therapy with ASCT
	6. Total bilirubin $\leq 2 \times$ the upper limit of the normal range (ULN).
	7. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
	8. Calculated creatinine clearance $\geq$ 20 mL/min (MDRD formula should be used for calculating creatinine clearance values)
	9. Female patients who:
	  - Have been postmenopausal for at least 2 years before the screening visit, OR
	  - Are surgically sterile, OR If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
	  - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

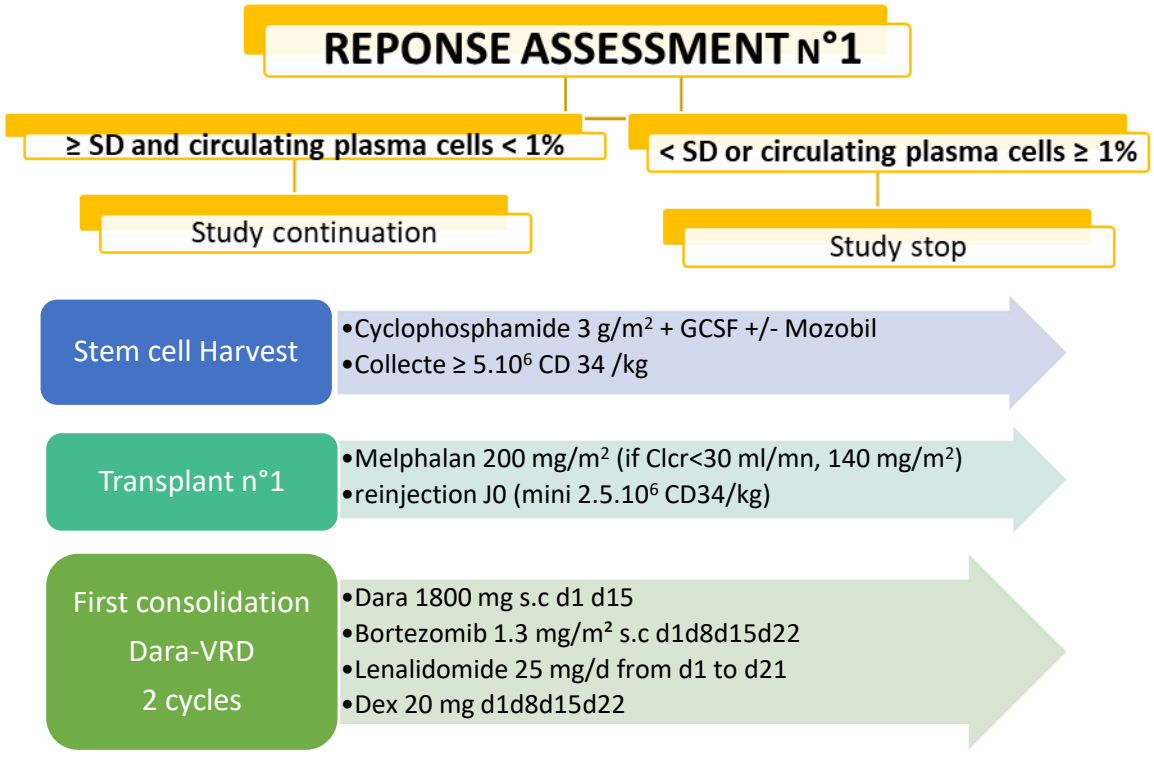
	10. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following: - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable methods of contraception.) 11. Patients agree - not to share study medication with any other person and to return all unused study drugs to the investigator. - to abstain from donating blood while taking the study drug therapy and for one week following discontinuation of the study drug therapy. 12. Must be able to adhere to the study visit schedule and other protocol requirements 13. Affiliated with an appropriate social security system.
Exclusion criteria	1. Male or female patients <18 or >69 years old 2. History of malignancy within 3 years before the date of inclusion (exceptions are squamous and basal cell carcinomas of the skin, carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the coordinating Investigatior, is considered cured with minimal risk of recurrence within 3 years) 3. Prior history of symptomatic myeloma with previous chemotherapy for myeloma except corticotherapy (dexamethasone 40 mg/d for 4 days max). 4. Any other uncontrolled medical condition or comorbidity that might interfere with subject's participation. 5. Pregnant or breast feeding females 6. Known positive for HIV 7. Known seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as a viremia at least 12 weeks after completion of antiviral therapy) 8. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects 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 PCR. 9. Patient with severe renal failure that require dialysis and clairance creatinine < 20 ml/min 10. Prior local irradiation within two weeks before first dose. However, an exception (that is patients allowed to remain in the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not by themselves fulfil a criterion for disease progression.) 11. Evidence of central nervous system (CNS) involvement 12. Unable to take corticotherapy, daratumumab, bortezomib and or lenalidomide at study entry. 13. Ongoing active infection, especially ongoing pneumonitis 14. Ongoing Cardiac dysfunction: specify e.g. uncontrolled hypertension, MI within 6 months, unstable Angina pectoris, Cardiac arrhythmia Grade 2 or higher 15. Patients with a left ventricular ejection fraction under to 40 % (LVEF <40%). 16. Use of any other experimental drug or therapy within 15 days of screening. 17. Any >grade 2 toxicity unresolved 18. Inability or unwillingness to comply with birth control requirements 19. Unable to take antithrombotic medicines at study entry 20. Major surgery within 14 days before enrolment. 21. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. 22. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. 23. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of daratumumab and lenalidomide including difficulty swallowing 24. Adult under guardianship, curatorship or any legal protection
Investigational medicinal product(s)	Bortezomib, Daratumumab, Lenalidomide and Dexamethasone
Expected benefits for the participants and for society	The pPCL patients included in this phase 2 study present a form of with ultra-high risk multiple myeloma, a specific population associated with poor outcome after standard therapy. The high efficacy of the VRD combination has been previously described, even in the context of intensive therapy with autologous stem cell

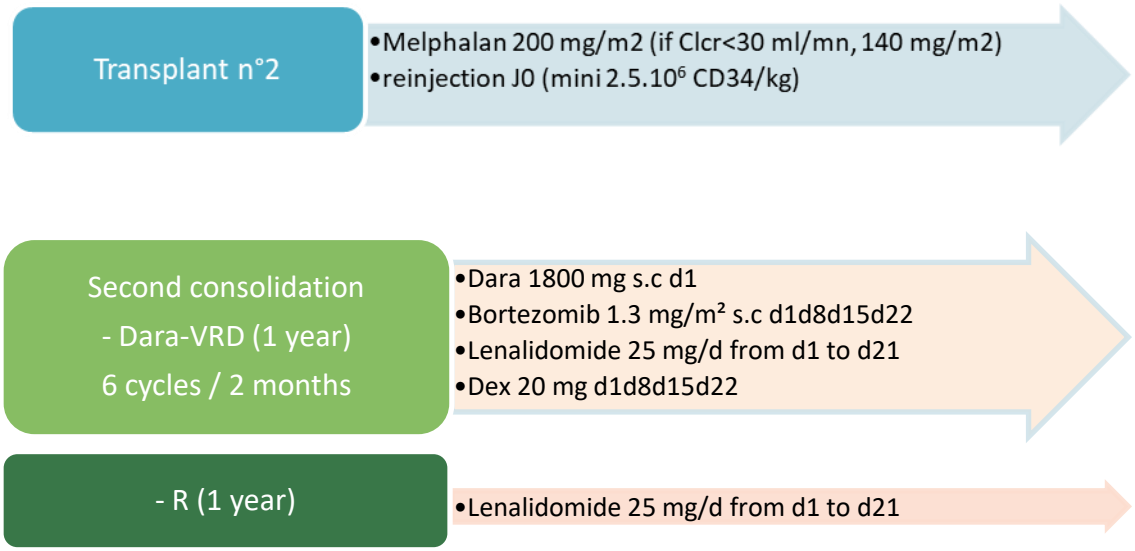
	transplant (see above). The safety and efficacy of daratumumab in combination with other myeloma agents has been confirmed in the context of large phase 3 trials in both relapsed and de novo myeloma patients. Overall, patients treated in this program with quadruplet VRD daratumumab induction and consolidation plus tandem autologous stem cell transplantation expect an individual benefit in terms of quality of response, duration of response, and survival.
Risks and burdens added by the study	The safety of Dara-VRD as induction and consolidation therapy in the context of intensive therapy with autologous stem cell transplant has also been reported (Blood, 2020). This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines.
Number of participants included	29
Number of centres	16 French sites (IFM sites) are planned
Duration of the study	81 months Enrolment of subjects will be completed in approximately 33 months. Subjects will be treated during 36 Months, and followed 12 months after
Number of enrolments expected per site and per month	Due to the rarity of the disease, it is not possible to predict the number of enrolments per site: 1 or 2 patients are expected per site during the enrolment period.
Statistical analysis	The primary endpoint of the trial is the VGPR or better rate at completion of induction phase (according to the IMWG response criteria). In our previous published phase II trial 36% of patients achieved VGPR or better after induction. Using a phase 2 one stage A'Hern design, with a lowest acceptable response rate of 35% (p0) and an expected response rate of 60% (p1), with type 1 and type 2 error levels of 5% and 20%, 26 patients are needed. To account for 10% of non-evaluable patients, 29 patients will be recruited.
Funding sources	- PHRC-K 2018 - Pharmaceutical companies will provide the study drugs: Subcutaneous Daratumumab and Lenalidomide
Study will have a Data Safety Monitoring Board	*Yes*

4 STUDY OVERVIEW DIAGRAM





REPONSE ASSESSMENT N°2



5 SCIENTIFIC JUSTIFICATION FOR THE STUDY

Plasma cell leukaemia is a rare variety of multiple myeloma with severe prognosis. The IMWG recently revised the diagnostic criterion of primary PCL to ≥ 5% circulating plasma cells in peripheral blood smears [Fernández de Larrea C et al, 2021]. These leukemias can be either primitive when it is the first manifestation of the disease or secondary in a refractory or relapsed myeloma context. It is a rare disease: primitive plasma cell leukemia (PCL) accounting for less than 2% of diagnosed myeloma. Hepatosplenomegaly with lymphadenopathy, thrombocytosis, low serum monoclonal component, renal insufficiency or extramedullary involvement are more commonly diagnosed than in multiple myeloma [Noel P et al, 1987; Dimopoulos MA et al, 1994].

Few data are currently available in the literature, both in terms of physiopathology and therapeutic management: these are retrospective series on a small number of patients. With conventional chemotherapy, the PCL prognosis remains severe with median survival rates reported between 7 and 14 months [Noel P et al, 1987]. Bortezomib-based regimens have shown promising results in small retrospective studies, and transplantation (auto and/or allograft) may improve OS for selected young patients [Fernandez de Larrea C et al, 2013].

The IFM group recently published a prospective study in 40 PCL patients, with Bortezomib-Dexamethasone-Doxorubicin/Cyclophosphamide (PAD/VCD) as induction before high dose Melphalan/ autologous stem cell transplantation (HDM/ASCT), followed by reduced intensity conditioning-allograft (RIC-Allo) or second HDM/ASCT plus consolidation/maintenance with Bortezomib-Lenalidomide-Dexamethasone/Lenalidomide. 27 patients (69%) responded to this induction (36% of them achieved a response ≥ VGPR); one patient underwent a syngeneic allograft and 25 HDM/ASCT: 16 of them subsequently received a RIC-allograft, 7 a second ASCT followed by maintenance. The median PFS and OS were 15 and 36 months respectively. OS seems to be superior in the double auto / maintenance group compared to the allotransplant group on landmark analysis (Royer et al, 2016).

The Italian group also recently reported a prospective trial in pPCL involving 23 patients treated with lenalidomide-dexamethasone: the median PFS and OS were 14 and 28 months, respectively. Nine of 15 patients eligible for transplant could receive HDM/ASCT and PFS and OS were 27 months and not reached, respectively (Musto P et al, 2014).
The aim of the present multicenter phase 2 study is to increase response rates and survival of pPCL patients with an intensive program including bortezomib–lenalidomide–dexamethasone

(VRD) plus daratumumab (Dara) as induction and prolonged consolidation therapy in the setting of double autologous stem cell transplant.

The design of the study is based on the following evidence-based knowledge:

- *High-Dose Therapy (HDT) is required for all transplant eligible patients, even in the era of new drug-containing regimen*

Several phase 3 trials performed in frontline MM patients, in the context of novel agent-based therapies, confirmed a progression-free survival (PFS) benefit associated with upfront ASCT. (Attal et al, 2017) (EMN02: Cavo et al, ASH2017). The PFS benefit was uniform across all the following subgroups: ISS stage I, II or III, standard or high-risk cytogenetics.

In pPCL patients, 2 large retrospective studies reported prolonged survival for young and selected patients with auto and/or allo-transplant (for EBMT group: Drake et a, 2010; for CIBMT group: Mahindra et al, 2012). More recently, the IFM and the Italian groups reported 2 prospective trials in the setting of new agents with encouraging survival outcomes (Royer et al, 2016; Musto et al, 2014). In the French study, there was a trend to a better survival for patients who underwent double transplant followed by prolonged consolidation and maintenance.

- *New drug-containing induction and consolidation regimens improve depth of response*

In the last 10 years, induction regimens dramatically changed following the onset of Thalidomide, Bortezomib and Lenalidomide, and various combinations of drugs are now available with high response rates. According to international guidelines, upfront therapy for transplant eligible MM patients should include triplet induction containing proteasome inhibitor (PI) and immunomodulatory agent (IMiD), autologous stem cell transplant, PI+IMiD based triplet consolidation and lenalidomide maintenance (Moreau et al, 2017). Unfortunately, despite this approach, virtually all MM patients experience disease relapse, especially those with High Risk (defined by adverse cytogenetic abnormalities: i.e. del (17p), or t(14;16) or t(4;14)) and with ultra-high risk criteria such as pPCL or extramedullary myeloma.

- *Lenalidomide maintenance improves survival*

A recent meta-analysis of controlled trials has shown that lenalidomide maintenance in MM was associated with a survival benefit following ASCT (McCarthy et al, 2017). The optimal duration of maintenance is still controversial. In the IFM 2005-02 study, the median duration of maintenance in the lenalidomide arm was 2 years, which appeared as a good compromise for safety and efficacy (Attal et al, 2012).

In the present study, all patients will receive 1-year lenalidomide consolidation.

- *Daratumumab can safely be combined with standard backbone myeloma regimens, for a long period of time with increased response rates and improved outcomes*

Daratumumab, an anti CD38 MoAb, is approved for the treatment of patients with relapsed MM on the basis of a large phase 2 trials (Lonial et al, 2016; Palumbo et al, 2016; Dimopoulos et al, 2016), and 2 phases 3 randomized trials (Castor and Pollux studies). Daratumumab's immediate and effective cell mediated cytotoxic effects against multiple myeloma cells, combined with the observed remarkable synergy with lenalidomide-bortezomib, may potentially improve the clinical outcome for patients with MM when combined with these agents in combination regimens. In the relapse setting, the Castor and Pollux trials confirmed the safety profile of daratumumab in combination with lenalidomide and bortezomib, and a strong benefit in terms of response rate and progression survival for patients in daratumumab arms. In previously untreated myeloma patients, the randomized phase 3 trial ALCYONE demonstrated the significant PFS advantage of the addition of daratumumab to the standard treatment melphalan – prednisone – bortezomib, followed by daratumumab maintenance with an excellent safety profile (Mateos et al, 2018). In the front-line setting, daratumumab is also currently tested in the randomized CASSIOPEIA trial in combination with VTD both prior to (induction) and following (consolidation) ASCT, and during maintenance with the aim of improving response rates and PFS (Moreau P Lancet 2019). In the same way, SC daratumumab was combined with VRD for transplant-eligible newly diagnosed MM patients in a phase 3 study, and improved depth of response, with no new safety concerns (Voorhees et al, 2020).

- *Rationale for Subcutaneous Daratumumab*

A new formulation of daratumumab for SC administration has been developed to avoid the long infusion time that frequently requires hospitalization with IV administration of daratumumab and to lessen the rate and severity of infusion-related reactions observed with IV daratumumab. Further, a recombinant human hyaluronidase PH20 (rHuPH20) was used to facilitate the SC administration in order to decrease the volume required for SC administration.

In the present study, daratumumab SC will be added at each step of the program, including induction and prolonged consolidation therapy.

5.1 BENEFITS AND RISKS FOR SUBJECTS TAKING PART IN THE STUDY

- **Benefits**

The pPCL patients included in this phase 2 study present with ultra-high-risk form of multiple myeloma, a specific population associated with poor outcome after standard therapy. The safety and efficacy of daratumumab in combination with other myeloma agents has been confirmed in the context of large phase 3 trials in both relapsed and de novo myeloma patients. Overall, patients treated in this program with quadruplet VRD daratumumab induction and consolidation plus tandem autologous stem cell transplantation expect an individual benefit in terms of quality of response, duration of response, and survival.

- **Risks**

The safety of Dara-VRD as induction and consolidation therapy in the context of intensive therapy with autologous stem cell transplant has been reported (Voorhees et al, 2020).
This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines.
The expected adverse reactions are listed in reference document: refer to the Summary of Product Characteristics.

6 OBJECTIVES

6.1 *Primary objective*

The primary objective is to determine the best overall Response rate at completion of induction phase (very good partial response or better)

6.2 *Secondary objectives*

The main secondary objective is to evaluate progression-free survival

The other secondary objectives are:

- to assess overall hematological response rates
- to evaluate overall survival
- to assess safety and toxicity according to NCI CTCAE
- to assess prognostic value of cytogenetic abnormalities of tumoral plasma cell
- to analyse the prognostic value of minimal-residual disease (MRD) by sequencing (NGS), after completion of induction, before second consolidation, before Len consolidation and at the end of treatment.
- to evaluate quality of life (EORTC QLQ-C30 domain scores)

7 STUDY DESIGN

7.1 *Study endpoints*

7.1.1 Primary endpoint

VGPR or better at the completion of induction phase (according to the IMWG response criteria).

The VGPR or better rate (as determined by the reviewer) is defined as the proportion of patients with confirmed IMWG criteria for VGPR, CR or stringent CR relative to the total number of patients in the ITT population. It will be presented along with its exact Clopper-Pearson 95%CI

7.1.2 Secondary endpoints

Major secondary endpoint:

Progression free survival (PFS) is defined as the time between the study enrolment and disease progression based on IMWG criteria or death on study, whichever occurred first.

Other secondary endpoints:

- Response rates (sCR, CR, VGPR, PR, SD): the response rate will be based on the response assessments determined by the IMWG criteria.
- Overall response rate (ORR) will be based on the patient's best response recorded from study enrolment until disease progression
- Overall survival (OS) is defined as the time between study enrolment and death due to any cause.
- Time to progression (TTP) is defined as the time between study enrolment and disease progression based on IMWG criteria.
- Duration of response (DOR) is defined as the time between initial documentation of a response and disease progression based on IMWG criteria.
- Assess safety by type, frequency, severity, relationship of adverse events to study treatment and changes in vital signs, physical exams. Incidence of Treatment Emergent Adverse Event (TEAE), Serious Adverse Event (SAE) and laboratory abnormalities using National Cancer Institute (NCI) common toxicity criteria (CCTAE V4).
- Evaluate response according to chromosomal structural abnormalities such as del(17p), t(4;14), t(11;14), t(14;16), t(14;20), amp(1q) and del(1p).
- MRD negative rate assessed by NGS is defined as proportion of subjects who have achieved MRD negative rate (<10^-6) at each timepoint of MRD assessment (after

completion of induction, before second consolidation before Len consolidation and at the end of treatment)

- Quality of life will be defined using EORTC QLQ-C30 domain scores at 3 timepoints: post induction, post ASCT n°2, end of second consolidation phase

7.2 *Description of research methodology*

7.2.1 Design of the study

This study is a multicentre open label single phase non comparative phase II study.

7.2.2 Number of participating sites

Sixteen French centers are planned (IFM sites).

7.2.3 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator, the patient will be included by connecting the eCRF. The patient identification number will be allocated

8 IMPLEMENTATION OF THE STUDY

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines.

8.1 *Informed consent*

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

8.2 *Study Procedures*

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-Up (PFS and OS). Refer to the flow-chart for the timing of assessments. Tests and procedures should be performed on schedule, but occasional

changes are allowable (± 3 days) for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study.
Additional details are provided as necessary in the sections that follow.

8.3 *Screening visit*

This visit may occur up to 21 days before the first study drug administration. The following procedures should be performed:

- Obtain subject informed consent form. Please specify in the patient application that one signed version of the informed consent form was given to the patient
- Assess inclusion /exclusion criteria
- Obtain medical subject history
- Record initial ISS score at diagnostic
- Specify that no prior history of neoplasia within the last 5 years and if so, please note that exclusion criteria has been verified
- Specify that Female patients are Not of Childbearing Potential (female patients are defined as NOT of childbearing potential if there is documentation of: a natural menopause for at least 24 consecutive months, or of a hysterectomy or bilateral oophorectomy). For all patients, please specify that they have been counselled about pregnancy precautions and risks of foetal exposure.
- Perform physical examination (write down weight and height in the patient file)Assess ECOG performance status
- Clinical Neurological exam
- Record prior treatments / procedures & prior anti-cancer therapies
- Record concomitant treatments / procedures
- Extramedullary plasmacytoma assessment: clinically AND by best radiography exam
- Obtain laboratory determinations: Complete blood count (CBC) including plasmocytes percentage and absolute value, blood chemistry and thyroid function test TSH.
- Perform Blood type and IAT
- Coagulation tests
- Serology (HIV, Hepatitis B and C).
- Perform β2-microglobulin analysis
- Perform a bone marrow aspirate to verify cytogenetic analysis (NGS) [To be analyzed by Toulouse Central Lab]
- Perform an electrophoresis and immunofixation of serum and urine (Bence Jones); obtain measurement of immunoglobulin free light chain

- Perform PET scanner (other exams skeletal survey and MRI, at physician discretion)
- Perform ECG and echocardiography.
- Bone marrow and blood collection for correlative studies (only upon patient consent): 10 mL of bone marrow aspirate will be collected in a purple top tube (EDTA) correlative study; 10 mL of blood will be collected in 1 purple top tube (EDTA)

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
the individual participating in the study	***the principal investigator or collaborating physician declared and trained in the study***	***screening visit***	**screening visit**

8.4 Baseline visit (treatment phase) or inclusion visit

The inclusion visit will be carried out by the physician who is responsible for the patient during the Study. During this visit, the investigator will:

- If all eligibility criteria are met the investigator will complete the Study Inclusion Form listing inclusion and exclusion criteria (e-CRF CleanWeb®)
- Perform the inclusion on CleanWeb®, an online system
- Perform a physical exam
- Assess ECOG performance status
- Perform a clinical Neurological exam
- Monitoring of thyroid function
- confirm absence of any SPM and thromboembolic events
- Obtain laboratory determinations (hematology including plasmocytes percentage and absolute value and blood chemistry),

8.5 Treatment phase visits

Please refer to study design and flowchart.

A special attention will be made on ANC and platelets determinations while on Daratumumab, bortezomib and Lenalidomide based on CBC evaluation at the start of each cycle. CBC will be done on a weekly basis during the first 2 cycles of induction.

<u>At day 1 of each cycle of treatment</u>

- Perform a physical exam (write down weight in the patient file)
- Assess ECOG performance status
- Clinical Neurological exam
- Confirm absence of any SPM and thromboembolic events
- Record any AE (in the patient file as in the CRF, provide grade, determine whether it is attributable to study treatment, specific treatment of the AE if any)
- Extramedullary plasmacytoma assessments: clinically every day 1 of cycles
- Dispense study drug
- Perform drug accountability (to write down in the patient file)
- Record concomitant treatments / procedures
- Serum pregnancy test (sensitivity of 25 mIU/mL) must be completed for females of childbearing potential with regular or no menstrual cycles. Weekly for the first 21 days of study participation and then every 21 days while on study during the first 17 cycles, then every 28 days during maintenance at study discontinuation, and at day 28 following study drug discontinuation. Urine pregnancy test allowed if results from a serum pregnancy test will not be promptly available.

– Monitoring of thyroid function : every 6 months

- Obtain laboratory determinations (hematology including plasmocytes percentage and absolute value and blood chemistry),
- Perform an electrophoresis and immunofixation of serum and urine (bence jones); obtain measurement of immunoglobulin free light chain [analyzed locally at d1 of each cycle]
- Bone marrow aspirate and 10 mL of blood:
    - o To be performed if the patient reaches CR as per the IMWG criteria [local laboratory].
    - o To be performed for MRD, for patient in VGPR or better, after completion of induction, before second consolidation, before first part (Dara-VRD) of second consolidation, before second part of second consolidation (Len consolidation) and at the end of treatment.
    - o To be performed at relapse
- Response assessment [on the basis of on local lab], to write down in the patient file and the CRF.
- Response assessment: patients who discontinue from the study for other reason than PD, will have response assessed on a 3 months-basis frequency until PD or until start of further myeloma therapy. Date of progression will be provided for these patients in the patient file and the CRF.

- ***Disease assessment (local assessment) will be performed at the end of the induction to determine if patient continue with the study or not***.

- Responding patients (response ≥ SD and circulating plasma cell < 1 %) => pursuit of the study
- Non-responding patient (response < SD or circulating plasma cell ≥ 1 %) => off study

Subjects who cannot proceed to stem cell mobilization at this timepoint, based on investigator discretion or institutional practice, will be withdrawn from treatment. Subjects with disease progression will also be withdrawn from treatment. These subjects will enter the follow-up phase.

8.6 Last study visit (end of treatment visit)

- To be done at 28 days post last cycle of consolidation (lenalidomide).
- Perform a physical exam (write down weight in the patient file)
- Assess ECOG performance status
- Clinical Neurological exam
- Extramedullary plasmacytoma assessment: clinically AND by best radiography exam comparative to screening and to best response
- Record any SAE (in the patient file as in the CRF, provide grade, determine whether it is attributable to study treatment, specific treatment of the AE if any)
- Record SAE concomitant treatments / procedures and anti-myeloma therapies.
- Perform an electrophoresis and immunofixation of serum and urine (bence jones); obtain measurement of immunoglobulin free light chain
- Obtain laboratory determinations (hematology including plasmocytes percentage and absolute value and blood chemistry)
- Bone marrow aspirate for MRD and 10 mL of blood
- Response assessment [on the basis of on local lab], to write down in the patient file and the CRF
- Serum pregnancy test (sensitivity of 25 mIU/mL) must be completed for females of childbearing potential at day 28 following study drug discontinuation

8.7 Follow-up visits

Post treatment follow-up: participants will be followed as per institutional practice on every three months basis during the follow up period after completion of consolidation until disease progression or up to 3 years after the last patient has been enrolled.

Patients who stop treatment for any reason other than progressive disease will continue to have progression-free follow-up visits. The progression-free follow-up should occur every 12 weeks until the occurrence of progression. All subsequent antineoplastic therapies will be recorded, regardless if they are initiated before or after progressive disease. Patients who start an alternative antineoplastic therapy prior to disease progression will continue to be followed for progression.

Patients who stop treatment due to progressive disease will continue to have overall survival visits/assessments. During the OS follow-up, assessments can be made over the phone and do not require a clinic visit. The OS follow-up should be conducted every 12 weeks after documented progressive disease until death or termination of the study by the sponsor. All subsequent antineoplastic therapies will be recorded during the OS follow-up period.

Information for new primary malignancy should be collected during the study, including the PFS and OS follow-up periods.

NOTE: Related SAEs must be reported to the Sponsor Pharmacovigilance. This includes deaths that the investigator considers related to study drug that occur during the post treatment follow-up. In addition, new primary malignancies that occur during the follow-up periods, irrespective of causality to study regimen, must be reported to Sponsor pharmacovigilance.

8.8 Early termination visit

- Perform a physical exam (write down weight in the patient file)
- Assess ECOG performance status
- Clinical Neurological exam
- Extramedullary plasmacytoma assessment: clinically AND by best radiography exam comparative to screening and to best response
- Record any SAE (in the patient file as in the CRF, provide grade, determine whether it is attributable to study treatment, specific treatment of the AE if any)
- Record SAE concomitant treatments / procedures and anti-myeloma therapies.
- Perform an electrophoresis and immunofixation of serum and urine (Bence Jones) to confirm PD. Obtain measurement of immunoglobulin free light chain if needed, to be confirmed with 2 samples in local lab [local lab]
- Obtain laboratory determinations (hematology and blood chemistry)
- Serum pregnancy test (sensitivity of 25 mIU/mL) must be completed for females of childbearing potential at study discontinuation.

- Progression assessment according to local lab reports, and write down the exact date of progression in the patient file and the CRF. Progression must be confirmed in local lab with a second sample at ANY TIME [local lab].

8.9 Expected length of participation and description of the chronology and duration of the study.

The total duration of the Study will be 81 months:

- Expected duration of inclusions: 33 months.
- Duration of participation of each patient: 48 months
    - Maximum period between screening and enrolment: 21 days
    - Treatment duration: 36 months

8.10 End of trial

End of trial is defined by the last visit of the last included patient. It should take place 48 months after inclusion of the last patient.

8.11 Table or diagram summarising the chronology of the study

Procedures		Screening	Cycles 1 and 2				Cycle 3 and 4				MHSC	HDM/ASCT n°1	First Conso (Dara-VRD x2 cycles)				HDM/ASCT n°2	Conso 2 (Dara-VRD x 6 cycles)				Conso/Len (12 months)	EOT visit	Progression visit	Follow-up
			D 1	D8	D15	D22	D 1	D8	D15	D22			D 1	D8	D15	D22		D 1	D8	D15	D22	D1			
screening procedures	Obtain subject informed consent form	X																							
	Assess inclusion/exclusion criteria	X																							
	Obtain medical subject history	X																							
	Record prior treatments and procedures	X																							
	Record prior anti-cancer therapies	X																							
physical assessments	Physical examination	X	X				X				X	X	X				X	X				X	X	X	
	Quality of life	X									X							X					X		
	Clinical Neurological exam	X										X					X						X	X	
	ECOG performance status	X	X				X				X	X	X				X	X				X	X	X	
	Extramedullar plasmacytoma assessment	X	X				X				X					X	x	X				X	X	X	

Procedures		Screening	Cycles 1 and 2				Cycle 3 and 4				MHSC	HDM/ASCT n°1	First Conso (Dara-VRD x2 cycles)				HDM /ASCT n°2	Conso 2 (Dara-VRD x 6 cycles)				Conso/Le n (12 months)	EOT visit	Progressio n visit	Follow -up
			D 1	D8	D15	D22	D 1	D8	D15	D22			D 1	D8	D15	D22		D 1	D8	D15	D22	D1			
local laboratory	Hematology (ANC, platelet count)	X	X	X	X	X	X		X		X	X	X				X	X				X	X	X	
	Rénal fonction, Electrolytes	X	X	X	X	X	X		X		X	X	X				X	X				X	X	X	
	Percentage and absolute value of circulating plasma cells	X	X				X				X	X	X				X	X				X	X	X	
	Calcemia	X	x				X				X	X	X				x	x				X	X	X	
	Hepatic function	X	x				X				x	x	x				X	x				X	X	X	
	LDH serum	X	x				x				x	x	x				x	x				X	X	X	X
	Thyroid test (TSH)	X									X						X[i]					X	X		
	B2 microglobuline	X																							
	CRP	X																							
	Troponine and bnp	X	X				X				x	X	X				X	X							
	Serum Pregnancy Test (if indicate)	X	X				X				X	X	X				X	X					X	X	
	Electrophoresis of serum and urine, M-component measurement [local lab]	x	X				x				X	x	x				x	x				X	X	X	X
	Ig free light chain [local lab]	X	X				x				X	x	x				x	X				X	X	X	X
	Blood type and IAT	X																							

	Procedures	Screening	Cycles 1 and 2				Cycle 3 and 4				MHSC	HDM/ASCT n°1	First Conso (Dara-VRD x2 cycles)				HDM /ASCT n°2	Conso 2 (Dara-VRD x 6 cycles)				Conso/Le n (12 months)	EOT visit	Progressio n visit	Follow -up
			D 1	D8	D15	D22	D 1	D8	D15	D22			D 1	D8	D15	D22		D 1	D8	D15	D22	D1			
Central lab	Cytogenetics [central lab]	X																							
	MRD test –NGS [a]	X									X[a]							X[a]				X[a]	X[a]		
Procedures	Bone marrow aspirate	X									X						X	X				X	X		
	Stem cell collection										x														
	TEP scanner	X									X+						X*								
	12-leads ECG	X									X						X								
	Echocardiography	x									X						X								
	Response assessment						X				X		X				X	X				X	X		X
	Adverse events		X				X				X	X	X				X	X				X	X	X	X
	Concomitant therapies/procedures	X	X				X					X	X				X	X				X	X	X	X
	Survival, post study treatment																								X
Study Drugs	Study drug dispensation, patient diary		X				X						X					X				X			
	Daratumumab S.Cut		X	X	X	X	X		X				X		X			X							
	Bortezomib S Cut		D1 + D4	D8 + D11			D1 + D4	D8 + D11					X	X	X	X		X	X	X	X				

Procedures	Screening	Cycles 1 and 2				Cycle 3 and 4				MHSC	HDM/ASCT n°1	First Conso (Dara-VRD x2 cycles)				HDM /ASCT n°2	Conso 2 (Dara-VRD x 6 cycles)				Conso/Len (12 months)	EOT visit	Progression visit	Follow-up
		D 1	D8	D15	D22	D 1	D8	D15	D22			D 1	D8	D15	D22		D 1	D8	D15	D22	D1			
Lenalidomine dispensation (21/28 days cycles)		X *(treatment from D1 to D21)*				X *(treatment from D1 to D21)*						X *(treatment from D1 to D21)*					X *(treatment from D1 to D21)*				X *(treatment from D1 to D21)*			
Dexamethasone oral/IV dosing		D1D2	D8D9	D15D16	D22D23	D1D2	D8D9	D15D16	D22D23			X	X	X	X		X	X	X	X				
Melphalan Administration											X					X								
Cyclophosphamide administration										X														
Drug accountability		X				X					X	X				X	X				X	X		

X* : standard of care

MRD test –NGS [a] : only for patient in VGPR or better

8.12 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments		Dara-VRD, Lenalidomide
Visits	*Treatment visits during induction, ASCT and consolidation*	
Biology	*Hematoly, biochemical exams, Bone marrow aspiration for cytogenetics at screening visit*	*Bone marrow aspiration for MRD at MHSC, at D1 of Conso 2 at D1 of len Conso, at the end of treatment*
Imaging	*TEP, TDM, IRM Echocardiography*	

8.13 Biological samples collection

Samples (serum, DNA) taken collected as part of the standard of care will be stored in a biological sample collection at the laboratory of Toulouse Central Lab (IUCT Oncopole, Toulouse) under the supervision of Pr. Hervé AVET-LOISEAU for a period of 10 years.

Fish analysis take part of the standard of care; a part of the samples will be used for MRD assessment for this study.

At the end of the study, the samples will be kept.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition (myeloma / plasma cell leukaemia) in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research [and to the director of the competent regional healthcare authority if the entity is a health establishment] (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

9 ELIGIBILITY CRITERIA

9.1 Inclusion criteria

1. Male or female patients 18 to 69 years old.
2. Patient with primary plasma cell leukemia disease as defined by the International Myeloma Working Group (IMWG 2021) (Annexe I)

3. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care
4. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
5. Eligible for high dose Melphalan therapy with ASCT
6. Total bilirubin $\leq 2 \times$ the upper limit of the normal range (ULN).
7. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
8. Calculated creatinine clearance $\geq$ 20 mL/min MDRD formula should be used for calculating creatinine clearance values
9. Female patients who:

- Have been postmenopausal for at least 2 years before the screening visit, OR
- are surgically sterile, OR If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

10. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

11. Patients agree

- not to share study medication with any other person and to return all unused study drugs to the investigator.
- to abstain from donating blood while taking the study drug therapy and for one week following discontinuation of the study drug therapy.

12. Must be able to adhere to the study visit schedule and other protocol requirements
13. Affiliated with an appropriate social security system

9.2 Exclusion criteria

1. Male or female patients <18 or > 69 years old

2. History of malignancy within 3 years before the date of inclusion (exceptions are squamous and basal cell carcinomas of the skin, carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the coordinating investigator, is considered cured with minimal risk of recurrence within 3 years)
3. Prior history of symptomatic myeloma; with previous chemotherapy for myeloma except corticotherapy (dexamethasone 40 mg/d for 4 days max).
4. Any other uncontrolled medical condition or comorbidity that might interfere with subject's participation.
5. Pregnant or breast feeding females
6. Known positive for HIV
7. Known seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as a viremia at least 12 weeks after completion of antiviral therapy)
8. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects 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 PCR.
9. Patient with severe renal failure that require dialysis and clearance creatinine < 20 ml/min
10. Prior local irradiation within two weeks before first dose. However, an exception (that is patients allowed to remain in the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not by themselves fulfil a criterion for disease progression.)
11. Evidence of central nervous system (CNS) involvement
12. Unable to take corticosteroid therapy, daratumumab, bortezomib and or lenalidomide at study entry.
13. Ongoing active infection, especially ongoing pneumonitis
14. Ongoing Cardiac dysfunction: specify e.g. uncontrolled hypertension, MI within 6 months, unstable Angina pectoris, Cardiac arrhythmia Grade 2 or higher, NYHA class III/IV
15. Patients with a left ventricular ejection fraction under to 40 % (LVEF <40%).
16. Use of any other experimental drug or therapy within 15 days of screening.
17. Any >grade 2 toxicity unresolved
18. Inability or unwillingness to comply with birth control requirements
19. Unable to take antithrombotic medicines at study entry

20. Major surgery within 14 days before enrolment
21. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
22. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
23. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of daratumumab and lenalidomide including difficulty swallowing.
24. Adult under guardianship, curatorship or any legal protection

9.3 Recruitment procedure

All participating centers services specialized in oncology and haematology. Patients will be recruited as they are followed in these centres since the diagnosis of primary plasma cell leukaemia: 29 patients will be enrolled in this study.

	Number of participants
Total number of participants to be included	***29***
Number of centres	***16***
Enrolment period (months)	***36***
Number of participants/centre	***1,8***
Number of participants/centre/month	***<1***

9.4 Termination rules

9.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)

- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

9.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment).
- premature exit from the study will not affect the participant's ongoing care and the participant will have standard care .
- In case of serious adverse events, see the corresponding section on vigilance

9.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.

In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1.

9.4.4 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:
first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the four treatment arms, requiring a reassessment of the benefit-risk ratio for the study if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy Similarly, AP-HP, as the sponsor, or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.
The AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.
If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Research Ethics Committee within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

10 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

10.1 *Treatment phase*

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules.
The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression, completion of the planned treatment, or for the other reasons outlined below.
Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed, then the subject will discontinue the study drugs, complete the End-of- Treatment Visit, and enter the Follow-up Phase.

Induction treatment (cycles 1 - 4)

After inclusion, screening and biological samples collection, patients will receive Dexamethasone 40mg/day for 4 days.
According to local practice, one dose of doxorubicine (30 mg/m² IV) or cyclophosphamide (750 mg/m² IV) may also be added to reduce the tumoral mass and minimize the risk of tumor lysis

syndrome (TLS). In this case, investigators need to refer to the updated SmPCs of these products for contraception recommendation.

Subjects should be monitored for symptoms of TLS. Management of TLS, including increasing hydration and treating hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. It is also recommended that subjects be treated prophylactically in accordance with local standards (eg, increased hydration; allopurinol 300 mg daily and medication to increase urate excretion).

Patients will receive 4 × 28 days cycles of Dara-VRD; each cycle and supporting treatment are described in the Study Diagram.

Pre-mobilization assessment

For subjects not experiencing disease progression, subjects may proceed to stem cell mobilization. Subjects who cannot proceed to stem cell mobilization at this timepoint, based on investigator discretion or institutional practice, will be withdrawn from treatment. Subjects with disease progression will also be withdrawn from treatment. These subjects will enter the follow-up phase.

Mobilization and harvesting stem cells (HSC) (3 weeks after the last dose of lenalidomide)

Following initial therapy with Dara-VRD, patients will undergo collection of autologous PBSCs.

Intensification with ASCT1

Participants will undergo conditioning for autologous PBSC transplant with melphalan.

First Consolidation (within 2 months after ASCT1) (cycles 5-6)

Consolidation therapy may commence when engraftment is complete and when the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (2 months post ASCT1). Patients will receive 2 × 28 days cycles of Dara-VRD: each cycle and supporting treatment are described in the Study Diagram.

Pre-melphalan

For subjects not experiencing disease progression, subjects may proceed to ASCT2. Subjects who cannot proceed to ASCT2 at this timepoint, based on investigator discretion or institutional practice, may enter the second consolidation phase treatment. Subjects with disease progression will be withdrawn from treatment and enter the follow-up phase.

Intensification with ASCT2

Participants will undergo conditioning for autologous PBSC transplant with melphalan.

Second consolidation (within 2 months after ASCT2)

Consolidation therapy may commence when engraftment is complete and when the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (2 months post ASCT2). Patients will receive 6 × cycles of Dara-VRD (1 cycle every 2 months), then 1 year of Lenalidomide (21 days / 28 days): each cycle and supporting treatment are described in the Study Diagram

End of treatment (EOT):

Patients will attend an End of Treatment (EOT) visit 28 days after receiving their last dose of study drug and will continue to be followed for other follow-up assessments specified in the Schedule of events.

10.2 *Description of the investigational medicinal product(s)*

10.2.1 Investigational medicinal product 1: BORTEZOMIB

The PCl-2 study is an institutional trial sponsored by APHP, a non-profit organization.
Bortezomib in combination with dexamethasone is indicated for this research population under reimbursable conditions. Patients have this treatment as part of their standard of care as recommended by 2019 IFM guidelines.
So their providing complies with the French article L1121 -16- 1 of the Code of Public Health. This article allows the investigational medicinal products allowed, by the competent authority, to be covered by the national health insurance funds. They will not be provided by the sponsor and will be prescribed on a standard care prescription to facilitate their management.
In accordance with Good Practices Guidelines and to track the treatment given to each patient, all the information related to the treatment (batch traceability...) will be collected. Adapted support will be established (patient's notebook).
The dispensary pharmacist will track all items relating to the dispensing (date of dispensation, number of units delivered, presentations, batch numbers, expiry dates, and identity of the person delivering the treatment). The pharmacist will also add the following information: PCL-2 AP-HP, patient ID on each box.

The compliance monitoring sheet (in patient's note book) will be filled by the patient or the nurse. Patient's note book will be returned with the prescription by the patient with empty, filled or opened boxes at the follow up visit

Treatment

Subjects will receive 1.3 mg/m² bortezomib as a SC injection. On treatment days when both bortezomib and daratumumab are administered, bortezomib must be administered after the daratumumab administration.
If a subject's weight changes by more than 10% from baseline, the dose of bortezomib will be re-calculated. Bortezomib dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there must be at least 72 hours between doses of bortezomib. Skipped doses of bortezomib will not be made up later in the cycle

Administration

Bortezomib will be given as a sub cutaneous injection for 1.3 mg/m² doses

During **Induction**, Bortezomib 1.3 mg/m² will be administered on Days 1, 4, 8 and 11 for each four 28 days-cycles.

During **First and Second Consolidation**, Bortezomib 1.3 mg/m² will be administered on Days 1, 8, 15 and 22.

Note that during the first phase of consolidation, cycles will be given for 2 x 28 days cycles.

Note that during the second phase of consolidation, cycles will be given each 2 months for a total of 6 cycles.

Dose adjustment

Dose adjustments of bortezomib will follow the approved labeling as follows:

- Starting dose: 1.3 mg/m^2
- Dose level -1: 1.0 mg/m^2
- Dose level -2: 0.7 mg/m^2
- Dose level -3: discontinue bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib as noted in table 2.

10.2.2 Investigational medicinal product 2: LENALIDOMIDE

Lenalidomide will be provided by the sponsor.
Lenalidomide will be provided to study's centres by the DEC-AGEPS as boxes blister cards of 21 capsules of 5 or 10 mg.

Each blister card will be labelled according European regulation for investigational medicinal products.

Blister cards should be store at a temperature below 25°C, with temperature monitoring and control.

Treatment

Lenalidomide will be given as a single, daily oral dose of 25 mg (induction, consolidations) for a total of 21 days out of a 28-day cycle (or at dose adjusted for renal function as per below).

Administration of lenalidomide will be at approximately the same time each day. Patients should be instructed to swallow lenalidomide capsules whole with water and not to break, chew, or open the capsules.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Administration

During **Induction and different phases of consolidation**, lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 days cycle.

Dose adjustment

Dose adjustments of lenalidomide will follow the approved labeling as follows:

- Starting dose: 25 mg
- Dose level -1: 20 mg
- Dose level -2: 15 mg
- Dose level -3: 10 mg
- Dose level -4: 5 mg
- Dose level -5: Discontinue lenalidomide permanently

Dose adjustments should be based on the highest grade of toxicity that is ascribed to

lenalidomide as noted in table 2.

10.2.3 Investigational medicinal product 3: DARATUMUMAB

Daratumumab will be provided by the sponsor. Daratumumab will be provided to study's centres by the DEC-AGEPS as 1800 mg vials of solution for SC injection.

Each vial will be labelled according European regulation for investigational medicinal products.

Vials should be stored at 2-8°C, with temperature monitoring and control.

Daratumumab Subcutaneous Preparation

Dara-SC will be provided as a fixed-dosed (1800 mg), combination drug product containing rHuPH20 (= Recombinant human hyaluronidase PH20) drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

Administration

Daratumumab (1800 mg) will be administered by SC injection by manual push over 3 to 5 minutes in the abdominal SC tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections.

Daratumumab will be given once every week for Cycles 1 to 2, then every 2 weeks for Cycles 3 and 4 of **Induction** and during **First Consolidation** (2 cycles).

During **Second Consolidation**, Daratumumab once every 8 weeks for 1 years (for a total of 6 cycles).

Every effort should be made to keep subjects on the planned dosing schedule. However, doses given within 3 days of the scheduled dose are permitted, as long as the interval between doses is at least 5 days.

Pre-infusion medication

Pre-medications for daratumumab will be administered as described in the Time and Events Schedules: subjects will receive the following medications prior to injection:

- *Paracetamol* (acetaminophen) 650-1000 mg IV or orally (PO) up to 3 hours prior to

daratumumab injection.

- *An antihistamine* (H1 receptor antagonist according to institutional standard) up to 3 hours prior to injection.

- *Montelukast* should be given up to 3 hours prior to daratumumab administration. 10mg is required on Cycle 1 Day 1 and optional for all other doses of daratumumab.

- *Dexamethasone* is also required pre-injection during maintenance (20 mg up to 3 hours prior daratumumab injection).

Post-infusion medication

For subjects with higher risk of respiratory complications (eg, subjects who have a FEV1 < 80%), patients with mild asthma or mild COPD, the following post-infusion medications should be considered:

- *Antihistamine*

- *Short-acting β2 adrenergic receptor agonist such as salbutamol*

- *Control medications for lung disease* (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD).

- corticosteroid : during consolidations phase according to Darzarlex smpc

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If, after 4 full doses, an at- risk subject experiences no major infusion-related reactions, then these post-infusion medications may be stopped at the investigator’s discretion.

<u>Dose adjustment</u>

Dose modification of Dara (increase or decrease) is not permitted.

Dose delay is the primary method for managing daratumumab-related toxicities. On the first day of each new treatment cycle and before each dose of study drug, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 5. Cycle delays will be based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

The study treatment must be held if any of the following criteria are met, to allow for recovery from toxicity, regardless of relationship to study drug:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia

- Grade 3 or higher thrombocytopenia

- Febrile neutropenia

- Neutropenia with infection, of any grade

- Grade 3 or higher non-hematologic toxicities with the following exceptions:

    - Grade 3 nausea that responds to antiemetic treatment within 7 days

    - Grade 3 vomiting that responds to antiemetic treatment within 7 days

    - Grade 3 diarrhoea that responds to antidiarrheal treatment within 7 days

    - Grade 3 fatigue that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

    - Grade 3 asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab.

Study treatment should be resumed when the toxicity has resolved to ≤ Grade 2. If study drug administration does not commence within the prespecified window of the scheduled administration date (Tables below), then the dose will be considered a missed dose.

Administration may resume at the next planned dosing date. A missed dose will not be made up.

Daratumumab administration schedule for Induction

Cycles	Frequency	Dose Held	Dosing restart
1 and 2	weekly (q1wk)	>3 days	Next planned weekly dosing date
3 and 4	Every 2 weeks (q2wks)	>7 days	Next planned every 2 weeks dosing date

Daratumumab administration schedule for **First Consolidation**

Cycles	Frequency	Dose Held	Dosing restart
5 and 6	Every 2 weeks (q2wks)	>7 days	Next planned every 2 weeks dosing date

Injection-related Reactions

Subjects should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the IPPI for further details. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be permanently discontinued.

Injection-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR adverse event to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.

Injection-related Reactions of Grade 3 or Higher

For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point daratumumab administration may be restarted at the investigator's discretion. Please refer to the IPPI for further details regarding continuation of daratumumab administration.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the subject must be permanently discontinued from daratumumab treatment.

For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject must be permanently discontinued from daratumumab treatment.

Local Injection-site Reactions

In Study MMY1004 Part 1, SC administration of daratumumab in abdominal SC tissue was associated with local injection-site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

Hepatitis B virus (HBV) Reactivation

Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with daratumumab. HBV screening must be performed in all patients before initiation of treatment with daratumumab. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of daratumumab treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated. In patients who develop reactivation of HBV while on daratumumab, suspend treatment with daratumumab and institute appropriate treatment. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Daratumumab interference with Indirect Antiglobulin Test (IAT) results

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to

daratumumab administration) or genotypically matched units

b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs.

Uncross matched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant haemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab Investigator's Brochure.

10.2.4 Investigational medicinal product 4: DEXAMETHASONE

The PCl-2 study is an institutional trial sponsored by APHP, a non-profit organization.
Dexamethasone is used in the therapeutic indication of his marketing authorization. So their providing complies with the French article L1121 -16- 1 of the Code of Public Health.

This article allows the investigational medicinal products allowed, by the competent authority, to be covered by the national health insurance funds. They will not be provided by the sponsor and will be prescribed on a standard care prescription to facilitate their management.
In accordance with Good Practices Guidelines and to track the treatment given to each patient, all the information related to the treatment (batch traceability...) will be collected. Adapted support will be established (patient's notebook).
The dispensary pharmacist will track all items relating to the dispensing (date of dispensation, number of units delivered, presentations, batch numbers, expiry dates, and identity of the person delivering the treatment). The pharmacist will also add the following information: PCL-2 AP-HP, patient ID on each box.
The compliance monitoring sheet (in patient's note book) will be filled by the patient or the nurse. Patient's note book will be returned with the prescription by the patient with empty, filled or opened boxes at the follow up visit

Treatment

Dexamethasone will be administered IV or PO at a total dose of 40 mg weekly (20 mg/day over 2 days during induction, 20 mg/day during consolidation).

Administration

During **Induction**, Dexamethasone 20mg/day will be administered on days 1-2, 8-9, 15-16 and 22-23 of each 28 days cycle (4 Cycles).

During **First Consolidation**, Dexamethasone 20mg/day will be administered on days 1, 8, 15 and 22 of each 28 days cycle (2 Cycles).

During **Second Consolidation**, Dexamethasone 20mg/day will be administered on days 1, 8, 15 and 22 of each 2 months cycle (6 Cycles).

Dose adjustment

If a weekly dexamethasone dose is missed, it may be taken if < 4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

Dexamethasone may be reduced, if necessary (see table 2).

10.3 *Dose reductions/adjustments*

Dose Delays and Dose Modifications

Bortezomib, lenalidomide and dexamethasone doses may be reduced, or the treatment schedule may be modified for the management of the study drug-related toxicities.

Cycle Delay

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 5. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle. For any neurological deficits that develop, it is strongly recommended that these be evaluated by the same physician who performed the neurological assessment at baseline. The parameters in Table 1 must be met on the first day of a new cycle (ie, the following represent baseline inclusion criteria levels):

Table 1: Re-treatment Criteria Before the Start of Each Induction/Consolidation Cycle

Laboratory parameter	Requirements before each study agent administration
ANC	≥1.0 x 10^9/L
Platelet count	≥70 x 10^9/L
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L)

If the above parameters are not met, the start of the next cycle will be held for a minimum of 1 week and a maximum of 28 days until recovery to the specified levels. Supportive care medications including transfusions should be administered at the investigator discretion. During the cycle delay, daratumumab, bortezomib, dexamethasone and lenalidomide, (all applicable) must be held.

Subjects must have adequate hematologic recovery (ANC≥1.0 x 10^9/L and platelets ≥ 75 x 10^9/L) following ASCT prior to initiating consolidation therapy.

Table 2: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 OR 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, restart VRD. Reduce by 1 dose-level the suspected medication(s) AND implement appropriate anti-allergic prophylaxis therapy. If the reaction was anaphylactic in nature, do not resume VRD. NOTE: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue VRD.		
Cardiovascular	Fluid Retention (ie, edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed, and decrease dexamethasone dose by 1 dose-level; if edema persists despite above measures, decrease dose another dose-level. Permanently discontinue dexamethasone if symptoms persist despite second dose reduction.
Constitutional	Fatigue[a] ≥ Grade 3 (ie, severe fatigue interfering with activities of daily living)	Hold the dose until resolved to Grade ≤2. Consider reduction of lenalidomide or bortezomib by 1 dose-level or change to bortezomib dosing once per week.		
Cutaneous	Non-blistering rash Grade 2	Hold bortezomib therapy. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib. Restart with lower concentration formulation. If recurrent consider IV bortezomib.	Consider holding lenalidomide.	
	Non-blistering rash ≥ Grade 3 or 4	Hold bortezomib and lenalidomide therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib and lenalidomide and continue antihistamines and/or low-dose steroids as per institutional practice. Restart with lower concentration formulation. If recurrent, consider IV bortezomib. For grade 4 toxicity, permanently discontinue bortezomib and lenalidomide permanently.		
	Desquamating (blistering) rash- any grade or erythema multiform ≥ Grade 3	Discontinue bortezomib and lenalidomide permanently. Hold other therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart other medications.		
Gastrointestinal	Constipation[b] ≥ Grade 3	Hold bortezomib therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
	Diarrhea[c] ≥ Grade 3	Hold bortezomib and consider loperamide therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		
	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)			Treat with histamine-2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose-level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)			Hold dexamethasone and consider treatment with histamine-2 blockers, sucralfate, or proton pump inhibitor. Restart and reduce dexamethasone by 1 dose level if symptoms are adequately controlled. If symptoms persist despite above measures, permanently discontinue dexamethasone.
	Acute Pancreatitis			Permanently discontinue dexamethasone.
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G-CSF.	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other haematologic toxicities present ore recurrent episode reduce lenalidomide by 1 dose level.	
	Grade 3 neutropenia associated with fever (≥38.5ºC) or Grade 4neutropenia	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other haematologic toxicities present reduce lenalidomide by 1 dose level. Maintain bortezomib at current dose. If recurrent episode, reduce both lenalidomide and bortezomib by 1 dose-level.		

Body System	NCI-CTC Adverse Event and or Symptom and Category		Bortezomib	Lenalidomide	Dexamethasone
	Thrombocytopenia Grade 3 (without complications)		No dose reduction required for bortezomib.	Reduce lenalidomide by 1 dose-level for the remainder of the cycle.	
	Platelet count ≤30 x 10^9/L or ANC ≤0.75 x 10^9/L on a bortezomib dosing day		Hold bortezomib dose.		
	Platelet count <25,000/µL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding		Hold therapy with all drugs until recovery to baseline OR ≤Grade 2. Upon recovery, reduce bortezomib 1 dose level, hold lenalidomide for remainder of the cycle and decrease by 1 dose level at start of next cycle.		
Infection	Herpes Zoster[d] activation or reactivation ANY grade		Hold ALL therapies until lesions are dry. If not already underway, begin antiviral treatment Once the infection is resolved, all medications can be restarted without a dose reduction; however, continued antiviral prophylaxis is required.		
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)				Decrease dexamethasone dose by 1 dose-level. If weakness persists despite above measures, decrease dose by 1 *further* dose-level. If symptoms *still* persist, permanently discontinue dexamethasone
Metabolic	Hyperglycemia ≥ Grade 3				Treatment with insulin or oral hypoglycemics. If uncontrolled despite above measures, decrease dose by 1 dose-level until levels are satisfactory.
Neurological[e]	Peripheral Neuropathy (Sensory or Motor) and/or Neuropathic Pain	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required.		
		Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Change schedule to once per week; if recurrence, reduce bortezomib by 1 dose-level		
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction by 1 dose-level and change bortezomib treatment schedule to once per week		
		Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Discontinue bortezomib permanently.		
	Progressive multifocal leukoencephalopathy (PRES)		In patients developing PRES, bortezomib should be discontinued	If PRES is confirmed, lenalidomide must be	

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
			permanently discontinued	
Neuro-psychological	Confusion or mood alteration >Grade 2 (interfering with function +/- interfering with activities of daily living)			Hold dexamethasone until symptoms resolve. Restart with 1 dose-level reduction. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Thromboembolic	Venous and /or pulmonary thrombo-embolism ≥ Grade 3 [Deep vein thrombosis or cardiac thrombosis intervention indicate; eg: anticoagulation, lysis, filter, invasive procedure.]		Stop until toxicity resolves and, if not already given, start anticoagulation therapy. Restart lenalidomide and dexamethasone at full dose after adequate anticoagulation.	
Renal Impairment	Moderate renal impairment- CrCl[f] 30-49 mL/min		Lenalidomide should be given at a dose of 10 mg daily[g]	
	Severe renal impairment- CrCl[f] <30 mL/min (not requiring dialysis)		Lenalidomide should be given at a dose of 15mg every 48 hrs[g]	
	End-stage renal disease- CrCl[f] <30 mL/min (requiring dialysis)		Lenalidomide should be given at a dose of 5mg[g] daily On dialysis days, administer dose after dialysis.	
Hepatic impairment	Moderate (bilirubin level > 1.5x-3xULN) or Severe (bilirubin level > 3xULN)	Reduce VELCADE to 0.7mg/m² in the first treatment cycle. Consider dose escalation to 1.0mg/m² or further dose reduction to 0.5mg/m² in subsequent cycles based on patient tolerability.		
Other toxicities	Any reported ≥ Grade 3	Determine drug attribution of the toxicity and hold the therapy(ies) as appropriate. If toxicity resolves to ≤ Grade 1, resume therapy with 1 level of dose reduction for suspect drug.		

[a] Determine if fatigue is possibly not medication-related but due to an underlying cause (eg, infection, progression of disease, diarrhea, anemia, depression) and treat these symptoms/causes as appropriate.
[b] Prior to dose reduction of medications, consider/eliminate other possible causes of constipation.
[c] Prior to dose reduction of medications, consider/eliminate other possible causes (ie, bacterial or viral infections) of diarrhea.
[d] In the event that a subject is already receiving antiviral treatment at the time of the Herpes Zoster activation, consider switching to or adding another antiviral agent.
[e] The neurotoxicity-directed questionnaire is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may require intervention or dose modification.
[f] CrCl = creatinine clearance. Estimated by creatinine clearance as calculated by the Cockcroft-Gault formula and adjusted for body weight in subjects with a body mass index >30 kg/m^2. The eGFR (MDRD) or CKD-epi formulas can also be utilized to assess renal function.
[g] Consider escalating dose to 15mg daily after 2 cycles if well tolerated.

10.4 *Non experimental product(s)*

10.4.1 Mobilization and Harvesting Stem Cells

After the 4 cycles of induction and disease evaluation, stem cell mobilization will be performed using cyclophosphamide (recommended dose of 3 g/m²) and stem cells will be harvested based on response to mobilization. The use of GCSF and Plerixafor are permitted per institutional practice: sufficient stem cells should be harvested to enable two transplants (≥ 5.10^6 CD34/kg).

10.4.2 High Dose Melphalan/ASCT n°1 and n°2

- Conditioning therapy: Mephalan 200mg/m^2

Although melphalan pharmacokinetics are not adversely affected by impaired renal function, the general toxicity of Melphalan 200 mg/m^2 total may be increased in patients with a creatinine clearance < 30 ml/min. For patients with a creatinine clearance < 30 ml/min, Melphalan dose should be reduced to 140 mg/m².

- Stem cell reinfusion: subjects will have a single re-infusion of stem cells

(minimum $2.5.10^6$ CD34/kg) 24-48 hours after high-dose melphalan (+ permitted tolerance)

- Support therapy will be administered according to local practice: G-CSF.

10.5 *Description of traceability elements accompanying the investigational medicinal product(s) (=IMPs)*

The pharmacist is responsible for ensuring adequate storage and management of all used and unused investigational medical product. This includes acknowledgement of receipt of each shipment of investigational medical product (quantity and conditions).
Daratumumab and lenalidomide accountability records will be provided to each study site in order to:
- Record the date of receipt, quantity, batch numbers, and expiry date of experimental medications
- Record the date, subject number, subject initials, quantity, batch numbers and expiry date of dispensed investigational drugs (*affixing if available the IMPs peel-off label on the prescription*).
- Record the date, quantity of used and unused medication.

For Bortezomib and Dexamethasone, the traceability of these IMPs will be made as described respectively in 10.2.1 and 10.2.4.

10.6 *Authorised treatments*

During **Induction**, the following supportive treatment will be associated:

- LMWH type Innohep® (4500 units per day) or equivalent,
- Anti zoster prophylaxis type Zelitrex® (500 mg twice daily) or equivalent,
- Anti infectious prophylaxis type Bactrim Forte® or equivalent (1 tablet three time a week) and Clamoxyl® or equivalent (1 g twice daily).
- Therapy for Tumor Lysis Syndrome: subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including increasing hydration and treating hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. It is also recommended that subjects be treated prophylactically in accordance with local standards (eg, increased hydration; allopurinol 300 mg daily and medication to increase urate excretion).

During **Consolidations**, the following supportive treatment will be associated:
- Anti thrombotic prophylaxis type Aspegic® or equivalent (100 mg daily),
- Anti zoster prophylaxis type Zelitrex® or equivalent (500 mg twice daily),
- Anti infectious prophylaxis type Bactrim Forte® or equivalent (1 tablet three times a week), and Clamoxyl® or equivalent (1 g twice daily).

10.7 *Prohibited treatments*

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma and other cancers is prohibited. Continuation of the study treatment during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression.
Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment.
Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (> 10 mg prednisone per day or equivalent) (other than those given for infusion-related reactions) should be avoided.
Nonsteroidal anti-inflammatory agents should be used with caution in order to prevent myeloma related kidney disease.
Administration of live virus vaccines should be excluded for patients receiving dexamethasone

Concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended.

10.8 *General consideration regarding treatments and specific warnings*

Investigators need to refer to the updated SmPCs of the marketing authorization of all drugs used in this clinical trial for the management of patients, in particular concerning contraindications, special warnings, precautions for use, contraception and monitoring of patients and drugs that are prohibited or to be used with precautions

10.8.1 Bortezomib

Heart failure: Patients with risk factors for or existing heart disease should be closely monitored

Pulmonary disorders: A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately.

Immunocomplex-mediated reactions: In case of serious reactions such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis, Bortezomib should be discontinued if occur.

Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

10.8.2 Lenalidomide

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Pulmonary hypertension: Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during lenalidomide therapy.

Hepatitis B reactivation: Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when lenalidomide is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy

Ophthalmic examination is required in case of visual troubles.

10.8.3 Dexametasone

Ophthalmic examination is required in case of visual troubles.

10.9 *Methods for monitoring compliance with the treatment*

Treatment administration will be done during hospitalization and compliance will be monitored. Nurses will complete a booklet to record administration in the booklet, the nurses will note every injection during treatment period, until hospitalization discharge and it will be kept in the patient's medical records + e-CRF.

10.10 *Special reporting and product Quality Complaint for Janssen product*

Special reporting situations and product quality complaints (PQCs) listed in the appendix have to be reported by the investigator to the CRA as soon as he is informed.
If one of these PQCs is associated with an SAE, follow the traditional SAE reporting system (see section "SAFETY ASSESSMENT").

11 EFFICACY ASSESSMENT

11.1 *Description of efficacy endpoints assessment parameters*

Patients will be assessed for disease response and progression according to the IMWG criteria for plasma cell leukemia. CR must be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum free light chains. One bone marrow assessment has to occur to document CR; no second bone marrow confirmation is needed

12 SPECIFIC STUDY COMMITTEES

12.1 Steering committee:

- Members of the committee: B Royer, J Lambert, L Briard, L Mameri, Hakeem F. Admane
- Missions: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study.
- Operating procedures: Propose procedures to be followed every 6 months during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority

13 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

13.1 *Recording and reporting adverse events*

13.1.1 Definitions

According to Article 2 of the Regulation (EU) N° 536/2014:

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.
The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

13.1.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the the intensity** of the adverse events:
- either by using general terms:
    - Mild: tolerated by the patient, does not interfere with daily activities
    - Moderate: sufficiently uncomfortable to affect daily activities
    - Serious: prevents daily activities
- or by using a rating scale for adverse events appended to the protocol (WHO)

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out)

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
**Or study procedures

13.1.3 Serious adverse events that require a notification without delay by the investigator to the sponsor

The investigator notifies the sponsor without undue delay but not later than within 24 hours on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and in the investigator's, brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalization or prolongation of existing hospitalization
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

13.1.4 Specific features of the protocol

13.1.4.1 Other events that require the investigator to notify the sponsor without delay

Adverse events deemed "medically significant"

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- **Second malignancies**

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy (SPM), regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the informed consent up to 5 years including any follow-up, observation and/or survival follow-up period(s) as applicable for this study. Events of second primary malignancy must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse

- **Transmission of infectious agent**

The investigator must notify the sponsor without delay on the day when the investigator becomes aware of suspected transmission of any infectious agent via administration of an investigational medicinal products

- **Drug exposure during pregnancy (paternal, maternal)**

The investigator must notify the sponsor without delay on the day when the investigator becomes aware of any exposure during pregnancy that occurs during the trial, even if not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

- **Females of Childbearing Potential:**

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of age or disease state) occurring while the subject is on IP, or within [insert time-frame which must be at least 28 days] of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy/ suspected pregnancy must be reported to the sponsor immediately by email, fax or phone and by sending a completed Pregnancy Report Form or approved equivalent Form to the sponsor.
The exposure of any pregnant female (e.g., caregiver or pharmacist) is also an immediately reportable event.
The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity, for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome) by email, fax or phone and by sending a completed Pregnancy Report Form or approved equivalent Form to the sponsor.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the Sponsor within 24

hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to the sponsor as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

- **Male Subjects**

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

- **Exposure while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.

Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

Adverse Events of Special Interest (AESI) for Daratumumab

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV Reactivation
- Other malignancies

13.1.4.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report forms**.**

- *Normal and natural course of the condition*:

- inpatient hospitalisation for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
- The progression disease with pain (grade < 3), hypercalcemia (grade < 3), anemia, infection (grade < 3)
- Cytopenia, mucositis, nausea, vomiting during autograft hospitalization

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

13.1.4.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant begins treatment with an investigational medicinal product/undergoes the first intervention specific to the study
- throughout the whole follow-up period required for the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

13.1.4.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

The investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
If it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

13.2 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

13.2.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,

All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

- For serious adverse events likely to be related to the investigational medicinal product(s): refer to the SmPC *or Investigator's Brochure* for daratumumab SC, bortezomib, lenalidomide and dexamethasone enclosed in appendix 18.5.

❖ For serious adverse events that may be related to the additional medicinal product(s):
- refer to the SmPC for cyclophosphamide and melphalan enclosed in appendix 18.5.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the competent authority:
in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction. The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;

The sponsor must provide all relevant additional information by sending follow-up reports within 8 calendar days following receipt.
in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and, in any event, not later than eight days after the initial report
All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.
Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

13.2.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

13.2.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,

- summary tables of all the serious adverse events that have occurred since the start of the study,
The sponsor produce one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.
The report must be submitted in CTIS no later than 60 days after the anniversary of the date corresponding to the date of authorization of the clinical trial by Competent Authority.

13.3 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority and to the Research Ethics Committee.

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Research Ethics Committee
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

14 DATA MANAGEMENT

14.1 *Data collection procedures*

Data will be collected by both the investigating along the trial in the source documents. They will also report these data in the CRFs. Trained data collectors (clinical research associates, CRAs) will check the CRFs for completion and correspondence with the source documents.

Data will be collected in real time. The co-ordinating centre will conduct an on-site visit and audit of data collection at each centre during the trial.

14.2 *Right to access data and source documents*

14.2.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the sponsor declare that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the

statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

14.2.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

14.2.3 Data confidentiality

The persons responsible for the quality control of clinical trials will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. *Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.*
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

14.3 Data processing and storage of research documents and data

14.3.1 Identification of the data processing manager and location(s)

The database will be handled by Prof. Matthieu Resche-Rigon, who will be responsible for data storage, the statistical analysis, and the tables and figures for the study report. He will be in close contact with the Data Safety and Monitoring Board and with the statistical editors of the journal to which the study report will be submitted for publication

14.3.2 Data entry

Non-identifying data will be entered electronically via a web browser.

14.4 *Data* ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

15 STATISTICAL ASPECTS

15.1 *Description of statistical methods to be used including the timetable for the planned interim analyses*

No interim is planned in this single-phase, phase II study.

All efficacy will be performed in the intent to treat (ITT) population, which include all patients included in the study.

All safety analyses will be based on the safety population. Safety population, will include all patients who received at least 1 dose of study drugs

Primary endpoint

The primary endpoint is the VGPR or better rate at the completion of induction phase (according to the IMWG response criteria) will be presented along with its exact Clopper-Pearson 95%CI.

Secondary endpoints

Major secondary endpoint:

The progression free survival (PFS) will be calculated as the time between the study enrolment and disease progression based on IMWG criteria or death on study, whichever occurred first. Subjects who withdrew for any reason will be censored on the date of their last adequate response assessment. PFS will be estimated non-parametrically using Kaplan Meier estimator. Predictive factors for PFS will be explored using relevant demographic and prognostic covariates by fitting a proportional hazard Cox model.

Other secondary endpoints:

- Response rates (sCR, CR, VGPR, PR, SD): the response rate will be based on the response assessments determined by the IMWG criteria. The statistical analysis of response rate will be based on the patient's response after induction regimen and during the treatment period, as determined by the reviewer, and estimated using the same methods as the primary endpoint
- The overall response rate (ORR) will be based on the patient's best response recorded from study enrolment until disease progression and will be calculated as the number of responders (at least partial response PR) divided by the number of subjects in the ITT population, and estimated using the same methods as the primary endpoint

- Overall survival (OS) is defined as the time between study enrolment and death due to any cause. Prognostic factor for OS will be explored. This endpoint will be analysed using the same methodology as the PFS endpoint.
- Time to progression (TTP) will be calculated as the months between the time from study enrolment and disease progression based on IMWG criteria. To take into account competing events (eg: death without progression), cumulative incidence of progression will be calculated within a competing risk frameworks
- Duration of response (DOR) will be calculated as the months between response and disease progression based on IMWG criteria. Analysis will be performed on the subset of patients obtaining response, and to take into account of competing events (eg: death without progression), cumulative incidence of lost of response will be calculated within a competing risk frameworks
- Quality of life (EORTC QLQ-C30 domain scores) will be described at each timepoint (post induction, post ASCT n°2, end of second consolidation phase) using median and interquartile range
- Prognostic value of MRD will be assessed by a landmark analysis: at each timepoint of MRD assessment, PFS (from MRD assessment to either progression or death) will be compared between MRD+ and MRD- patients using log rank test. Effect of MRD will be assessed by HR and its 95%CI, with adjustment of other prognostic variables of PFS using Cox model
- Safety analysis: descriptive statistics of cumulative dose, relative dose intensity, dose reduction and reason for dose reduction will be presented. Treatment emergent adverse events will be also presented. Overall adverse events will be summarized by System Organ Class (MedDRA dictionary) and Preferred Term and by severity (worst toxicity grade owing to the NCI CTC v4.0).

15.2 *Calculation hypotheses for the number of participants required and the result*

The primary endpoint of the trial is the VGPR or better rate at the completion of induction phase (according to the IMWG response criteria). In our previous published phase II trial 36% of patients achieved VGPR or better after induction. Using a phase 2 one stage A'Hern design, with a lowest acceptable response rate of 35% (p0) and an expected response rate of 60% (p1), with type 1 and type 2 error levels of 5% and 20%, 26 patients are needed. To account for 10% of non-evaluable patients, 29 patients will be recruited.

16 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial..

16.1 *General organisation*

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

16.1.1 Strategy for centre opening

The strategy for opening the sites is determined using the tailored monitoring plan. It will be performed by the CRA from the URC-DRC from Saint Louis hospital.

16.1.2 Scope of centre monitoring

In the case of this risk study **which is considered level D risk,** the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level « High ».

16.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the “source” documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

16.3 Case report forms

Electronic CRF:

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.

A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

16.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor’s procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

16.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

16.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals for France). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.
Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

Suitability of the facilities
Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

17 ETHICAL AND LEGAL CONSIDERATIONS

17.1 Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at screening visit.
The person will be granted a reflection period between the time when the subject receives the information and the time when he or she signs the consent form at screening visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to

the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.
At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. The sponsor will archive this envelope.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent in the cases stipulated in Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code) as well as the methods used for providing information with a view to obtaining their consent. The investigator will retain one copy of the signed and dated consent form.

17.2 Prohibition from participating in another clinical study or exclusion period set after the study

The participant may not enrol in another interventional study for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.
An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 30 days
The participants can however participate in other non-interventional studies.

17.3 Legal obligations

17.3.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Direction of Clinical Research and Innovation) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

17.3.2 Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Ethical Committee for this clinical trial on a medicinal product for human use, within the scope of its authority and in accordance with in force legislation and regulatory requirements.

17.3.3 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

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17.3.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology"

17.3.5 Amendments to the clinical trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the Ethics Committee and authorisation from competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

17.3.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation [to be defined otherwise if this is not the case].
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

17.3.7 Summary of the resultas of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to lay persons.

17.3.8 Archiving

Specific documents for a clinical trial involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the site who participated in the study;

- A sealed envelope for the sponsor, containing one copy of all information notes and consent forms signed by all individuals at the site who participated in the research;
- "Study" binders for the Investigator and the sponsor, containing:
    - the successive versions of the protocol (identified by the version no. and date), and any appendices
    - the Competent authority authorizations and Ethics Committee decisions
    - any correspondence
    - the enrolment list or register
    - the appendices specific to the research
    - final study report
- The data collection documents

18 FUNDING AND INSURANCE

18.1 *Funding sources*

PHRC Cancer (Hospital Funding for Clinical Research), 2018.
The following Investigational medicinal product are provided by companies:
o Lenalidomide -> Celgene
o Daratumumab -> Janssen Cilag
The Intergroupe Francophone du Myélome (IFM) funds and is responsible for the centralised measurement of MRD and transport of biological samples.

18.2 *Insurance*

Pursuant to Article L.1121-10 of the Code de la Santé Publique (French Public Health Code), insurance policies must guarantee the civil liability of the sponsor and that of any contributor and cover pecuniary consequences of damages arising from the study involving human participants.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

19 PUBLICATION RULES

19.1 *Mention of AP-HP affiliation for projects sponsored by AP-HP*

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym “AP-HP” first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

19.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- “The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l’Innovation)”

19.3 Mention of the financial backer in the acknowledgements of the text

“The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2018 (French Ministry of Health)”.

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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21 LIST OF ADDENDA

21.1 List of investigators

See enclosed document.

21.2 Serious Adverse Events notification form

See enclosed document.

21.3 IMWG 2021 criteria for plasma cell leukemia (PCL)

≥ 5% circulating plasma cells in peripheral blood smears

- ✓ Primary PCL: presents as de novo leukemia
- ✓ Secondary PCL: progression from a pre-existing multiple myeloma

IMWG response criteria for plama cell leukemia (Fernandez de Larrea C. et al, Leukemia 2013)

Response criteria for plasma cell leukemia

Category	*Bone marrow criteria*[a]	*Peripheral blood criteria*[a]	*Serological criteria*[b]	*Other criteria*
Stringent complete remission	Bone marrow plasma cells <5% and No malignant plasma cell by flow cytometry	No plasma cells in peripheral blood by flow cytometry	Negative serum and urine immunofixation Normal serum FLC ratio	Absence of extramedullary disease
Complete remission	Bone marrow plasma cells <5%	No plasma cells in peripheral blood	Negative serum and urine immunofixation[c]	Absence of extramedullary disease.
Very good partial response	Bone marrow plasma cells <5%	No plasma cells in peripheral blood	⩾90% reduction of serum M-protein and 24-h urinary M-protein <100 mg per 24 h[d]	Absence of extramedullary disease
Partial response	Bone marrow plasma cells–5 to 25%	Peripheral blood plasma cells from 1–5%	⩾50% reduction of serum M-protein and Reduction in 24-h urinary M-protein by ⩾90% and <200 mg per 24 h[e]	⩾50% reduction in the size of extramedullary disease
Stable disease	Not meeting the criteria of either partial response or progressive disease			
Progressive disease	>25% increase in plasma cells in a bone marrow aspirate or absolute increase ⩾10%	>5% absolute increase in peripheral blood plasma cells	>25% increase in the level of the serum monoclonal paraprotein with an absolute increase ⩾5 g/l >25% increase in the 24-h urinary light chain excretion with an absolute increase ⩾200 mg/24 h	Hypercalcemia Definite increase in lytic bone lesions Definite increase in the size or number of extramedullary disease
Relapse from complete remission	More than 10% increase in bone marrow plasma cells	Reappearance of peripheral blood plasma cells at any level	Reappearance of original M-protein in serum and/or urine immunofixation	Any extramedullary disease

Abbreviation: FLC, free light chain. [a]It is recommended that at least 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted. [b]It should be maintained for a minimum of 6 weeks. In case of discrepancy or undetectable serological parameter, the patient must be classified according to bone marrow criteria. [c]If the serum and urine M-protein are unmeasurable, a normal serum kappa/lambda FLC ratio is also required. [d]If the serum and urine M-protein are unmeasurable, a ⩾90% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-protein. [e]If the serum and urine M-protein are unmeasurable, a ⩾50% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-protein.

21.4 QLQ: EORTC QLQ-C30 (version3)

QUESTIONNAIRE SUR LA QUALITE DE VIE
EORTC QLQ-C30 version 3

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

Vos initiales : .....

Date de naissance : .....

La date d'aujourd'hui : .....

Au cours de la semaine passée	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
1. Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provision chargé ou une valise ?	1	2	3	4
2. Avez-vous des difficultés à faire une LONGUE promenade ?	1	2	3	4
3. Avez-vous des difficultés à faire un PETIT tour dehors ?	1	2	3	4
4. Etes-vous obligée de rester au lit ou dans un fauteuil la majeure partie de la journée ?	1	2	3	4
5. Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux W.C. ?	1	2	3	4
6. Etes-vous limitée d'une manière ou d'une autre pour accomplir, soit votre travail, soit vos tâches habituelles chez vous ?	1	2	3	4
7. Etes-vous totalement incapable de travailler ou d'accomplir des tâches habituelles chez vous ?	1	2	3	4

Au cours de la semaine passée	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
8. Avez-vous eu le souffle court ?	1	2	3	4
9. Avez-vous eu mal ?	1	2	3	4
10. Avez-vous eu besoin de repos ?	1	2	3	4
11. Avez-vous eu des difficultés pour dormir ?	1	2	3	4
12. Vous êtes-vous sentie faible ?	1	2	3	4
13. Avez-vous manqué d'appétit ?	1	2	3	4

14. Avez-vous eu des nausées (mal au cœur) ?	1	2	3	4
15. Avez-vous vomi ?	1	2	3	4
16. Avez-vous été constipée ?	1	2	3	4
Au cours de la semaine passée	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
17. Avez-vous eu de la diarrhée ?	1	2	3	4
18. Etiez-vous fatiguée ?	1	2	3	4
19. Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision ?	1	2	3	4
21. Vous êtes-vous sentie tendue ?	1	2	3	4
22. Vous êtes-vous fait du souci ?	1	2	3	4
23. Vous êtes vous sentie irritable ?	1	2	3	4
24. Vous êtes vous sentie déprimée ?	1	2	3	4
25. Avez-vous eu des difficultés pour vous souvenir de certaines choses ?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gênée dans votre vie FAMILIALE ?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gênée dans vos activités SOCIALES (par exemple sortir avec des amis, aller au cinéma…)	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers ?	1	2	3	4

POUR LES QUESTIONS SUIVANTES, VEUILLEZ REPONDRE EN ENTOURANT LE CHIFFRE ENTRE 1 ET 7 QUI S'APPLIQUE LE MIEUX A VOTRE SITUATION.

29. Comment évalueriez-vous l'ensemble de votre ETAT PHYSIQUE au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						Excellent

30. Comment évalueriez-vous l'ensemble de votre QUALITE DE VIE au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						Excellent

21.5 Lenalidomide Pregnancy prevention plan

Lenalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 1) provides the following information:
    - Potential risks to the fetus associated with lenalidomide exposure
    - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
    - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
    - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
    - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 2 and Section 3 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 4) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

1. LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

1.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

1.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

1.2. Counseling

1.2.1. Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 1.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

1.2.2. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

1.2.3. Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

1.3. Contraception

1.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation

- Partner’s vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

1.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

1.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

1.5. Pregnancy Precautions for Lenalidomide Use

1.5.1. Before Starting Lenalidomide

1.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

1.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

1.5.2. During and After Study Participation

1.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

1.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

1.5.3. Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

2. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

☐ NOT FCBP

2.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.

☐ That the required pregnancy tests performed are negative.

☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm

- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

2.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:

☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

3. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

<u>Do Not Dispense Lenalidomide if:</u>

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date:___/____/____ (dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

21.6 Special reporting and product Quality Complaint (PQCs) (Janssen Products)

Product Quality Complaint (PQC):
Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution. A complaint is any indication of the failure of the product to meet consumer or user expectations for quality or to meet performance specifications. It may allege an adverse reaction, injury, or malfunction associated with the use of the product. It may also involve the design, literature, packaging, advertising, availability, physical appearance, or promotion of a product.

Special reporting Situations:
The following special situations must be reported with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (paternal, maternal)
- Suspected transmission of any infectious agent via administration of a Janssen Product(s) under study.

The following special situations must be reported when associated with a serious adverse event (SAE):

- Overdose of Janssen Product(s) under study
- Exposure to Janssen Product(s) under study from breastfeeding
- Suspected abuse/misuse of Janssen product(s) under study
- Inadvertent or accidental exposure to Janssen Product(s) under study
- Any failure of expected pharmacological action (i.e., lack of effect) of Janssen Product(s) under study
- Medication error (includes potential, intercepted or actual) involving a Janssen product (with or without patient exposure to the Janssen Product(s) under study, e.g., name confusion)
- Unexpected therapeutic or clinical benefit from use of Janssen Product(s) under study

21.6 SmPC and Investigator's Brochure

- Investigational medicinal product 1: **BORTEZOMIB**
Cf. **SmPC of VELCADE®:**
https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_fr.pdf

- Investigational medicinal product 2: **LENALIDOMIDE**
Cf. **Investigator's Brochure** of Lenalidomide.

- Investigational medicinal product 3: **DARATUMUMAB**
Cf. **Investigator's Brochure** of Daratumumab.

- Investigational medicinal product 4: **DEXAMETHASONE**
Cf. **SmPC of NEOFORDEX®:**
https://www.ema.europa.eu/en/documents/product-information/neofordex-epar-product-information_fr.pdf
Cf. **SmPC of DEXAMETHASONE MYLAN 20 mg/5 ml, solution injectable en ampoule:**
http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=65822036&typedoc=R&ref=R0356492.htm