REGENERON HR-SMM:
Linvoseltamaba en monoterapia en HR-SMM

Linvoseltamab en HR-SMM

- Promotor REGENERON
- SIV planeadas y centros seleccionados por Regeneron

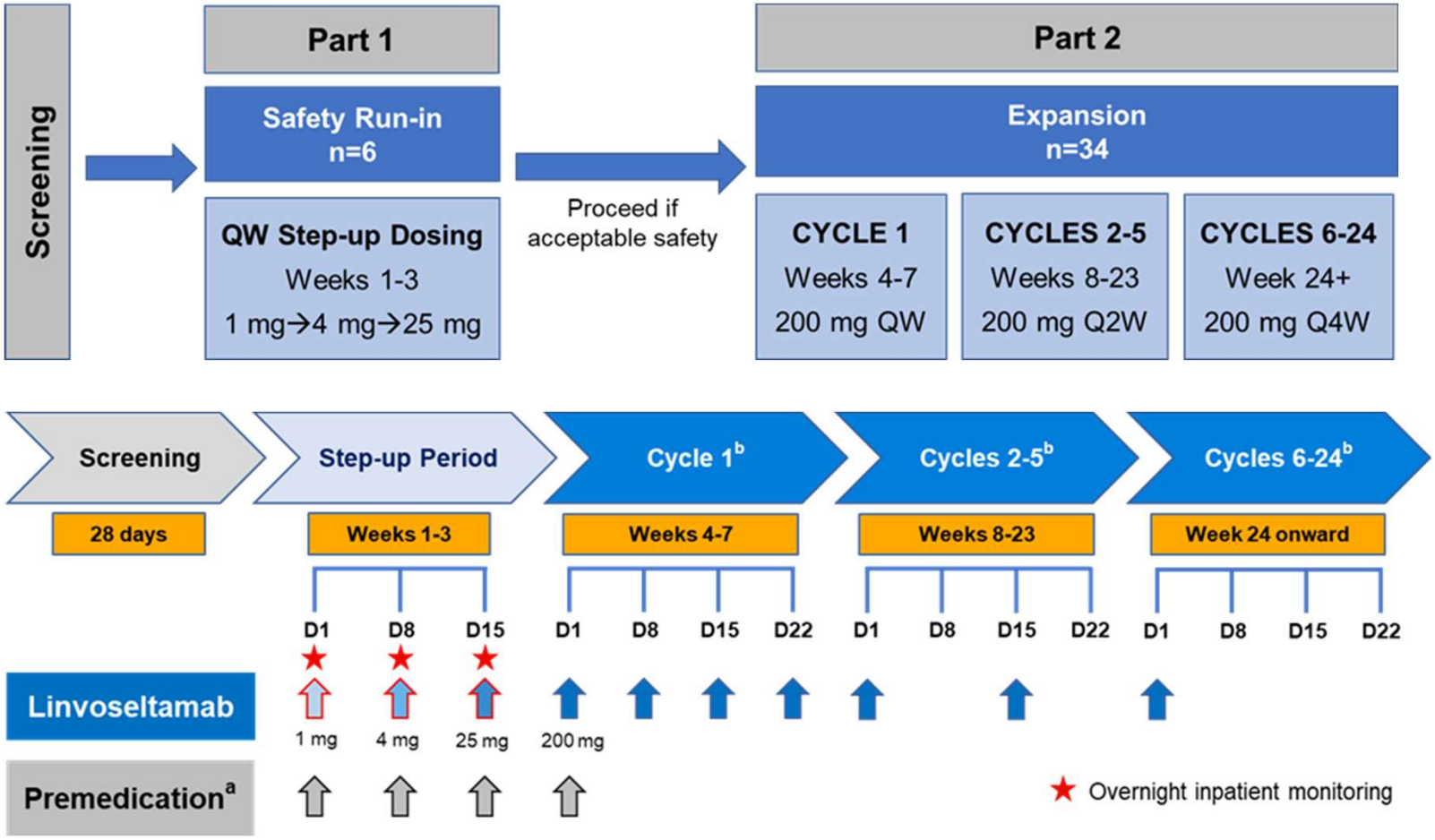
SMM diagnosis within 5 years of study enrollment per IMWG criteria defined as:

- Serum M-protein ≥30 g/L **or** urinary M-protein ≥500 mg per 24 hour **or** BMPCs 10% to <60% **AND** Absence of myeloma defining events or other related conditions (SLiM CRAB).
- High-risk SMM according to the following markers at screening:
  - At least 2 of the following abnormalities (Lakshman, 2018)
    - Serum M-protein >20 g/L or 2 g/dL
    - Serum involved/uninvolved FLC ratio >20
    - BMPCs >20%

  AND/OR

  - Both of the below findings (PETHEMA criteria):
    - ≥95% aberrant/clonal BMPCs
    - Immunoparesis defined as reduction of ≥1 uninvolved Ig isotype of at least 25% below the lower normal limit (only IgG, IgA and IgM will be considered)

Linvoseltamab en HR-SMM: Study flow and study design



Linvoseltamab en HR-SMM: study endpoints

Objective	
Primary	
Safety Run-In (Part 1): To evaluate the safety profile of linvoseltamab in participants with high-risk SMM	Frequency of AESI including grade 2 or higher CRS and ICANS assessed up to 5 years Frequency and severity of TEAEs assessed up to 5 years
Expansion (Part 2): To evaluate the efficacy of linvoseltamab in high-risk SMM participants, including those from the safety run-in cohort	CR rate as determined by the investigator using IMWG response criteria MRD negativity (10^{-5} sensitivity) at 12 and 24 months after the start of treatment

Linvoseltamab en HR-SMM: study endpoints

Secondary Applicable to both safety run-in and expansion unless otherwise specified	
To characterize the safety of linvoseltamab (Part 2)	Frequency of SAEs and severity of all AEs and lab abnormalities assessed up to 5 years
To evaluate the ORR	ORR as measured using IMWG criteria up to 3 years after end of treatment
To evaluate the DOR	DOR as measured using IMWG criteria up to 3 years after end of treatment
To evaluate biochemical PFS	Biochemical PFS as measured using IMWG criteria up to 3 years after end of treatment
To evaluate the proportion of participants with sustained MRD negativity	MRD negativity at the end of treatment and maintenance of MRD negativity up to 3 years after end of treatment
To evaluate the time to progression to MM	Time from treatment initiation to date of any myeloma defining event per SLiM CRAB diagnostic criteria (Table 2) assessed up to 5 years
To evaluate clinical PFS	Time from start of treatment to date of progression to MM or death, whichever happens first, assessed up to 5 years
To measure time to the start of systemic therapy for MM	Time to initiation of first-line treatment for MM assessed up to 5 years
To evaluate PFS after initiation of treatment for MM (PFS-2)	PFS from start of therapy for MM to date of progression or death, whichever happens first, assessed up to 5 years
To evaluate OS	OS as measured using IMWG criteria up to 3 years after end of treatment
To assess the ability to collect stem cells after linvoseltamab administration	Collection yield of CD34+ stem cells after treatment with linvoseltamab assessed up to 5 years
To characterize the PK properties of linvoseltamab	Concentrations of linvoseltamab in serum over time for the duration of treatment (up to 2 years)
To assess the immunogenicity of linvoseltamab	Incidence and titer of ADAs to linvoseltamab over time for the duration of treatment (up to 2 years)

Linvoseltamab en HR-SMM: Study endpoints

Objective	
Exploratory	
To evaluate changes in serum soluble BCMA levels	Concentrations of serum soluble BCMA levels during treatment with linvoseltamab
To assess serum M-protein by mass spectrometry and correlate with clinical response characteristics	Serum M-protein measurement by mass spectrometry over time
To evaluate CTCs	CTC levels and phenotype during treatment with linvoseltamab
To evaluate the effects of linvoseltamab on patient-reported health-related quality of life, functioning, and symptoms	Change from baseline in patient-reported symptoms, functioning, and global health status/quality of life per EORTC QLQ-C30 and EORTC QLQ-MY20 (2 global anchors PGIS and PGIC will be used to aid PRO interpretation)
To evaluate treatment effects of linvoseltamab on patient-reported overall impact of treatment toxicity as measured by the FACIT Item GP5	Change over time in patient-reported overall impact of treatment toxicity per the FACIT Item GP5
To evaluate healthcare resource use attributed to hospitalizations in participants receiving linvoseltamab	Number and duration of hospitalizations (including general ward, intensive care unit, emergency room visits) from start of study treatment to 90 days after last dose of study treatment
To characterize the immune profile of peripheral blood cells and bone marrow aspirate cells	Including, but not limited to, B, T, NK, and monocyte cell kinetics in blood and bone marrow over time
To evaluate the genomic determinants of SMM and progression to MM	Whole exome DNA and RNA sequencing of malignant plasma cells and bone marrow immune cells
To evaluate the effects of linvoseltamab on polyclonal immunoglobulins	Concentrations of IgA, IgM, IgG, IgD and IgE over time
To evaluate BCMA and other plasma cell antigens in bone marrow before and after treatment with linvoseltamab	BCMA and plasma cell antigen expression in bone marrow aspirates and biopsy