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A Study of Teclistamab in Combination with Daratumumab and Lenalidomide (Tec-DR) and Talquetamab in Combination with Daratumumab and Lenalidomide (Tal-DR) in Participants with Newly Diagnosed Multiple Myeloma

Submission date
11/10/2022

Recruitment status
Recruiting

Registration date
27/01/2023

Overall study status
Ongoing

Last Edited
30/10/2024

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Multiple myeloma (MM) is a blood cancer that forms in a type of white blood cells (WBCs) called plasma cells. Drugs that deviate T-cells (type of WBCs) to attack cancer cells may be an effective way to destroy them. Teclistamab and Talquetamab are modified antibodies (proteins made in the body against foreign matter) which bind to T-cells and MM cells, activate T-cells and lead to killing of MM cells. This study is designed to see if participants using Tec-DR or Tal-DR to treat MM will respond to treatment or whether treatment prolongs survival, and to assess if there are no detectable signs of cancer cells after treatment for a year (12-Month MRD negative CR), compared to DRd in participants with newly diagnosed MM who are either not eligible or for whom autologous stem cell transplant (ASCT)* is not planned as initial therapy.
*Collection and storage of a person's own healthy stem cells; given back to support intensive chemotherapy treatment.

Who can participate?
The study will include male and female participants 18 years or older.

What does the study involve?
This study consists of Screening, Treatment, and Followup Phases. Participants will receive either Tec-DR or DRd, as described below.
Tec-DR
• Teclistamab (Tec) – an injection under the skin administered with lower doses at first and then spaced over time according to the treatment dosing schedule.
• Daratumumab (D) - weekly in Cycles 1 and 2, Q2W on Days 1 and 15 of Cycles 3 to 6, Q4W on Day 1 of Cycle 7 and onward as an injection under the skin.

• Lenalidomide (R) - by mouth on Days 1 to 21 from Cycle 2 onwards.
• In addition, Dexamethasone is given by mouth or as an injection in a vein weekly in Cycles 2 to 3 only.

Tal-DR
• Talquetamab (Tal) – an injection under the skin administered with lower doses at first and then spaced over time according to the treatment dosing schedule.
• Daratumumab (D) - weekly in Cycles 1 and 2, Q2W on Days 1 and 15 of Cycles 3 to 6, Q4W on Day 1 of Cycle 7 and onward as an injection under the skin.
• Lenalidomide (R) - by mouth on Days 1 to 21 from Cycle 2 onwards.
• In addition, Dexamethasone is given by mouth or as injection in vein weekly in Cycles 2 to 3 only.

DRd
• Daratumumab (D) - weekly in Cycles 1 and 2, Q2W on Days 1 and 15 of Cycles 3 to 6, Q4W on Day 1 of Cycle 7 and onward as an injection under the skin.
• Lenalidomide (R) by mouth on Days 1 to 21 from Cycle 1 onwards.
• Dexamethasone (d) - by mouth or as an injection in a vein, weekly from Cycle 1 onwards.

Each cycle will consist of 28 days.
Participants will undergo study assessments such as blood and urine tests, imaging, bone-marrow testing, physical and neurological examinations, and questionnaires. The overall duration of the study will be up to 10 years (approximately).

What are the possible benefits and risks of participating?
There is no established benefit to participants of this study. Based on scientific theory, taking Tec-DR or Tal-DR may improve newly diagnosed MM. However, this cannot be guaranteed because Tec-DR and Tal-DR are still under investigation as treatments, and it is not known whether teclistamab in combination with DR will work, or whether talquetamab in combination with DR will work.
If participants are put in the DRd group, they will not receive teclistamab or talquetamab but will receive drugs already on the market.
Participants may experience some benefit from participation in the study that is not due to receiving study drug, but due to regular visits and assessments monitoring their overall health. Participation may help other people with newly diagnosed MM in the future.
Participants may have side effects from the drugs or procedures used in this study that may be mild to severe and even life-threatening, and they can vary from person to person. The most common, known risks are getting symptoms such as cytokine release syndrome (inflammation condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies), infections, injection-site reactions, cytopenia (reduction in blood cells), and hypogammaglobulinemia (low protein in blood that fights infection), immune effector cell-associated neurotoxicity syndrome (Neurological side effects may occur that include headaches or a condition), immune-related adverse event, skin and nail changes (talquetamab only; skin changes may include skin peeling, itching, and rash, and nail changes may include nail loss, peeling, ridging, discoloration, breaking and separation), oral toxicity (talquetamab only; dry mouth, altered taste, loss of taste, and difficulty swallowing) after getting the study drug. There are other, less frequent risks. The participant information sheet and informed consent form, which will be signed by every participant agreeing to participate in the study, includes a detailed section outlining the known risks to participating in the study.
Not all possible side effects and risks related to Tec-DR and Tal-DR are known at this moment. During the study, the sponsor may learn new information about Tec-DR and Tal-DR. The study doctor will tell participants as soon as possible about any new information that might make

them change their mind about being in the study, such as new risks.
To minimise the risk associated with taking part in the study, participants are frequently reviewed for any side effects and other medical events. Participants are educated to report any such events to the study doctor who will provide appropriate medical care. Any serious side effects that are reported to the sponsor are thoroughly reviewed by a specialist drug safety team.
There are no costs to participants to be in the study. The sponsor will pay for the study drug and tests that are part of the study. The participant will receive reasonable reimbursement for study-related costs (e.g., travel/parking costs).

Where is the study run from?
Janssen-Cilag International NV

When is the study starting and how long is it expected to run for?
October 2022 to August 2033

Who is funding the study?
Janssen Research and Development (UK)

Who is the main contact?
Emily Barton (Local Trial Manager) (UK)
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2022-000909-28

IRAS number
1005985

ClinicalTrials.gov number
NCT05552222

Secondary identifying numbers
64007957MMY3005, IRAS 1005985, CPMS 53049

Study information

Scientific Title
A phase III randomized study comparing teclistamab in combination with daratumumab SC and lenalidomide (Tec-DR) versus daratumumab SC, lenalidomide, and dexamethasone (DRd) in participants with newly diagnosed multiple myeloma who are either ineligible or not intended for autologous stem cell transplant as initial therapy

Acronym
MajesTEC-7

Study objectives
Current study hypothesis as of 14/09/2023:

1. Main objectives
To evaluate how effective Tec-DR (teclistamab [Tec] in combination with daratumumab [D] and Lenalidomide [R]) and Tal-DR (Talquetamab [Tal] in Combination with daratumumab [D] and Lenalidomide) are as compared to DRd (daratumumab[D], lenalidomide [R], and Dexamethasone

[d]).
2. Secondary objectives
2.1. To further evaluate how effective Tec-DR and Tal-DR are as compared to DRd.
2.2. To assess safety and tolerability of Tec-DR and Tal-DR.
2.3. To assess the pharmacokinetics (what the body does to the drug) and immunogenicity (immune response against the drug) of Tec and Tal.
2.4. To assess participant's symptoms, functioning, and quality of life with Tec-DR versus DRd and Tal-DR versus DRd.

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Previous study hypothesis:

The primary hypothesis of this study is that Tec-DR will significantly improve the rate of progression-free survival (PFS) or sustained minimal residual disease (MRD)-negative complete response (CR) compared with DRd in participants with newly diagnosed multiple myeloma who are ineligible or not intended for autologous stem cell transplant (ASCT) as initial therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval 23/01/2023, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley PA2 7DE, UK; +44 (0)141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 22/WS/0162

Study design
Randomized controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Multiple Myeloma

Interventions
Current interventions as of 14/09/2023:

Participants will receive either Tec-DR, Tal-DR or DRd, as described below. Central randomisation will be implemented in this study. Participants will be randomly assigned to 1 of 3 treatment groups based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.

Tec-DR Arm: Experimental: Teclistamab, Daratumumab SC, Lenalidomide (Tec-DR) Participants will receive teclistamab as subcutaneous (SC) injection in combination with daratumumab and lenalidomide.

Interventions:
Drug: Teclistamab
Teclistamab will be administered as SC injection.
Other Name: JNJ-64007957

Drug: Daratumumab
Daratumumab will be administered as SC injection.

Drug: Lenalidomide
Lenalidomide will be administered orally.

Tal-DR Arm: Experimental: Talquetamab, Daratumumab SC, and Lenalidomide (Tal-DR)
Participants will receive talquetamab as SC injection in combination with daratumumab and lenalidomide.
Interventions:

Drug: Talquetamab
Talquetamab will be administered as SC injection.
Other Name: JNJ-64407564

Drug: Daratumumab
Daratumumab will be administered as SC injection.

Drug: Lenalidomide
Lenalidomide will be administered orally.

DRd Arm: Active Comparator: Daratumumab SC, Lenalidomide, and Dexamethasone (DRd)
Participants will receive daratumumab as SC injection with lenalidomide and dexamethasone.
Interventions:

Drug: Daratumumab
Daratumumab will be administered as SC injection.

Drug: Lenalidomide
Lenalidomide will be administered orally.

Drug: Dexamethasone
Dexamethasone will be administered either orally or intravenously (IV).

Previous interventions:

Participants will receive either Tec-DR or DRd, as described below. Central randomisation will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.

Tec-DR Arm: Experimental: Teclistamab, Daratumumab SC, Lenalidomide (Tec-DR)
Participants will receive teclistamab as subcutaneous (SC) injection in combination with daratumumab lenalidomide.
Interventions:

Drug: Teclistamab
Teclistamab will be administered as SC injection.
Other Name: JNJ-64007957

Drug: Daratumumab
Daratumumab will be administered as SC injection.

Drug: Lenalidomide
Lenalidomide will be administered orally.

DRd Arm: Experimental: Daratumumab SC, Lenalidomide, and Dexamethasone (DRd)
Participants will receive daratumumab as SC injection with lenalidomide and dexamethasone.
Interventions:

Drug: Daratumumab
Daratumumab will be administered as SC injection.

Drug: Lenalidomide
Lenalidomide will be administered orally.

Drug: Dexamethasone
Dexamethasone will be administered either orally or intravenously (IV).

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Teclistamab, daratumumab, lenalidomide, dexamethasone, talquetamab

Primary outcome measure
Current primary outcome measure as of 30/10/2024:
1. Progression-free survival (PFS), defined as the time interval between the date of randomisation to the date of either progressive disease or death, whichever comes first, measured up to 9 years. Disease progression will be determined according to the International Myeloma Working Group (IMWG) response criteria.
2. 12-Month Minimal Residual Disease (MRD)-Negative Complete Response (CR), 12-month MRD-negative CR is defined as participants who achieve MRD-negative status at 12 months, as determined by next-generation sequencing (NGS) with sensitivity of 10^-5, prior to progressive

disease or subsequent anti-myeloma therapy and who also achieve CR or better, according to IMWG criteria.

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Previous primary outcome measure as of 03/01/2024 to 30/10/2024:
1. Progression-free survival (PFS), defined as the time interval between the date of randomisation to the date of either progressive disease or death, whichever comes first, measured up to 9 years. Disease progression will be determined according to the International Myeloma Working Group (IMWG) response criteria.
2. Complete response (CR) or better, defined as the percentage of participants achieving CR or stringent complete response (sCR) prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment, determined from randomisation up to 9 years.

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Previous primary outcome measure from 14/09/2023 to 03/01/2024:
1. Progression-free survival (PFS), defined as the time interval between the date of randomisation to the date of either progressive disease or death, whichever comes first, measured up to 9 years.
2. Sustained minimal residual disease (MRD)-negative complete response (CR), defined as participants who sustain MRD-negative status (determined by next-generation sequencing (NGS) with a sensitivity of 10^-5) for at least 12 months without any examination showing MRD positive status or progressive disease in between, assessed up to 9 years.

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Original primary outcome measure:
1. Progression-free survival (PFS), defined as the time interval between the date of randomisation to the date of either progressive disease or death, whichever comes first, measured up to 7 years.
2. Sustained minimal residual disease (MRD)-negative complete response (CR), defined as participants who sustain MRD-negative status (determined by next-generation sequencing (NGS) with a sensitivity of 10^-5) for at least 12 months without any examination showing MRD positive status or progressive disease in between, assessed up to 7 years.

Secondary outcome measures

Current secondary outcome measures as of 30/10/2024:
1. Very good partial response (VGPR) or better, defined as the percentage of participants achieving VGPR and CR (including stringent complete response [sCR]) prior to subsequent antimyeloma therapy in accordance with the International Myeloma Working Group (IMWG) criteria during or after the study treatment, determined from randomisation up to 9 years.
2. Complete response (CR) or better, defined as the percentage of participants achieving CR or stringent complete response (sCR) prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment, determined from randomisation up to 9 years.
3. Sustained minimal residual disease (MRD)-negative complete response (CR), defined as participants with CR or better who sustain MRD-negative status, as determined by next-generation sequencing (NGS) with a sensitivity of 10^-5, for at least 12 months without any examination showing MRD positive status or progressive disease in between, determined from randomisation up to 9 years.

4. MRD-negative CR, defined as the percentage of participants who achieve MRD-negative status, (determined by NGS with a sensitivity of 10^-5) at any time after randomisation and prior to progressive disease or subsequent antimyeloma therapy and who achieve CR or better, determined from randomisation up to 9 years.
5. Progression-free survival on next-line therapy (PFS2), defined as the time interval between the date of randomisation and the date of the event, which is defined as progressive disease as assessed by the investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first, measured from randomisation up to 9 years.
6. Overall survival (OS), defined as the time interval from the date of randomisation to the date of death due to any cause, measured from randomisation up to the date of death (up to 9 years).
7. Number of participants with adverse events (AEs) by severity determined from randomisation up to 9 years. An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product and does not necessarily have a causal relationship with the treatment. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The severity scale ranges from Grade 1 mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening, and Grade 5 death related to adverse event.
8.. Number of participants with abnormalities in laboratory parameters (serum chemistry and haematology) determined from randomisation up to 9 years.
9. Number of participants with abnormalities in vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure) determined from randomisation up to 9 years.
10. Number of participants with abnormalities in physical examination determined from randomisation up to 9 years.
11. Number of participants with abnormalities in electrocardiogram (ECG) determined from randomisation up to 9 years.
12. Serum concentrations of Teclistamab and Talquetamab measured by validated, specific and sensitive methods from randomisation up to 9 years.
13. Number of participants with anti-drug antibodies (ADAs) to Teclistamab and Talquetamab determined from randomisation up to 9 years.
14. Change from baseline in symptoms, functioning, and health-related quality of life (HRQoL) as assessed by a European organisation for research and treatment of cancer quality-of-life questionnaire core 30 (EORTC-QLQ-C30) determined from baseline up to 9 years. The EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea /vomiting), and 5 single symptom items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) and a single impact item (financial difficulties). The recall period is 7 days (“past week”), and responses are reported using verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale /item represents a high level of symptomatology/problems.
15. Change from baseline in treatment-related symptoms as assessed by patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE), determined from baseline up through to cycle 6 (each cycle of 28 days) (up to 196 days). The National Cancer Institute's (NCI's) PRO-CTCAE is an item library of common AEs experienced by people with cancer that are appropriate for self-reporting of treatment tolerability. Each symptom selected for inclusion can be rated by up to 3 attributes characterising the presence /frequency, severity, and/or interference of the AEs. It ranges from 0 to 4 with higher scores indicating higher frequency or greater severity /impact.
16. Change from baseline in symptoms, functioning, and overall HRQoL as assessed by EuroQol five dimension questionnaire 5-level (EQ-5D-5L), determined from baseline up to 9 years. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression plus a visual analogue scale rating “health today” with anchors ranging from 0 (worst imaginable) to 100 (best imaginable health state).
17. Time to sustained worsening in symptoms, functioning and HRQoL, defined as the time interval from the date of randomisation to the start date of meaningful change, measured from randomisation up to 9 years.

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Previous secondary outcome measures as of 03/01/2024 to 30/10/2024:

1. Very good partial response (VGPR) or better, defined as the percentage of participants achieving VGPR and CR (including stringent complete response [sCR]) prior to subsequent antimyeloma therapy in accordance with the International Myeloma Working Group (IMWG) criteria during or after the study treatment, determined from randomisation up to 9 years.
2. Sustained minimal residual disease (MRD)-negative complete response (CR), defined as participants with CR or better who sustain MRD-negative status, as determined by next-generation sequencing (NGS) with a sensitivity of 10^-5, for at least 12 months without any examination showing MRD positive status or progressive disease in between, determined from randomisation up to 9 years.
3. MRD-negative CR, defined as the percentage of participants who achieve MRD-negative status, (determined by NGS with a sensitivity of 10^-5) at any time after randomisation and prior to progressive disease or subsequent antimyeloma therapy and who achieve CR or better, determined from randomisation up to 9 years.
4. Progression-free survival on next-line therapy (PFS2), defined as the time interval between the date of randomisation and the date of the event, which is defined as progressive disease as assessed by the investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first, measured from randomisation up to 9 years.
5. Overall survival (OS), defined as the time interval from the date of randomisation to the date of death due to any cause, measured from randomisation up to the date of death (up to 9 years).
6. Number of participants with adverse events (AEs) by severity determined from randomisation up to 9 years. An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product and does not necessarily have a causal relationship with the treatment. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The severity scale ranges from Grade 1 mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening, and Grade 5 death related to adverse event.
7. Number of participants with abnormalities in laboratory parameters (serum chemistry and haematology) determined from randomisation up to 9 years.
8. Number of participants with abnormalities in vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure) determined from randomisation up to 9 years.
9. Number of participants with abnormalities in physical examination determined from randomisation up to 9 years.
10. Number of participants with abnormalities in electrocardiogram (ECG) determined from randomisation up to 9 years.
11. Serum concentrations of Teclistamab and Talquetamab measured by validated, specific and sensitive methods from randomisation up to 9 years.
12. Number of participants with anti-drug antibodies (ADAs) to Teclistamab and Talquetamab determined from randomisation up to 9 years.
13. Change from baseline in symptoms, functioning, and health-related quality of life (HRQoL) as assessed by a European organisation for research and treatment of cancer quality-of-life questionnaire core 30 (EORTC-QLQ-C30) determined from baseline up to 9 years. The EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional,

cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea /vomiting), and 5 single symptom items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) and a single impact item (financial difficulties). The recall period is 7 days ("past week"), and responses are reported using verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale /item represents a high level of symptomatology/problems.
14. Change from baseline in treatment-related symptoms as assessed by patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE), determined from baseline up through to cycle 6 (each cycle of 28 days) (up to 196 days). The National Cancer Institute's (NCI's) PRO-CTCAE is an item library of common AEs experienced by people with cancer that are appropriate for self-reporting of treatment tolerability. Each symptom selected for inclusion can be rated by up to 3 attributes characterising the presence /frequency, severity, and/or interference of the AEs. It ranges from 0 to 4 with higher scores indicating higher frequency or greater severity /impact.
15. Change from baseline in symptoms, functioning, and overall HRQoL as assessed by EuroQol five dimension questionnaire 5-level (EQ-5D-5L), determined from baseline up to 9 years. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analogue scale rating "health today" with anchors ranging from 0 (worst imaginable) to 100 (best imaginable health state).
16. Time to sustained worsening in symptoms, functioning and HRQoL, defined as the time interval from the date of randomisation to the start date of meaningful change, measured from randomisation up to 9 years.

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Previous secondary outcome measures from 14/09/2023 to 03/01/2024:

1. Very good partial response (VGPR) or better, defined as the percentage of participants achieving VGPR and CR (including stringent complete response [sCR]) prior to subsequent antimyeloma therapy in accordance with the International Myeloma Working Group (IMWG) criteria during or after the study treatment, determined up to 11 years.
2. Complete response (CR) or better, defined as the percentage of participants achieving CR or sCR prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment, determined for up to 11 years.
3. MRD-negative CR, defined as the percentage of participants who achieve MRD-negative status, (determined by NGS with a sensitivity of 10^-5) at any time after randomisation and prior to progressive disease or subsequent antimyeloma therapy and who achieve CR or better, determined up to 11 years.
4. Progression-free survival on next-line therapy (PFS2), defined as the time interval between the date of randomisation and the date of the event, which is defined as progressive disease as assessed by the investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first, measured up to 11 years.
5. Overall survival (OS), defined as the time interval from the date of randomisation to the date of death due to any cause, measured up to 11 years.
6. Number of participants with adverse events (AEs) by severity determined up to 11 years. An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product and does not necessarily have a causal relationship with the treatment. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening,

and Grade 5 death related to adverse event.
7. Number of participants with abnormalities in laboratory parameters (serum chemistry and haematology) determined up to 11 years.
8. Number of participants with abnormalities in vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure) determined up to 11 years.
9. Number of participants with abnormalities in physical examination determined up to 11 years.
10. Number of participants with abnormalities in electrocardiogram (ECG) determined up to 11 years.
11. Serum concentrations of Teclistamab and Talquetamab measured by validated, specific and sensitive methods up to 11 years.
12. Number of participants with anti-drug antibodies (ADAs) to Teclistamab and Talquetamab determined up to 11 years.
13. Change from baseline in symptoms, functioning, and health-related quality of life (HRQoL) as assessed by a European organisation for research and treatment of cancer quality-of-life questionnaire core 30 (EORTC-QLQ-C30) determined from baseline up to 11 years. The EORTC-QLQ-C30 Version 3 includes 30 items that makeup 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea /vomiting), and 5 single symptom items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) and a single impact item (financial difficulties). The recall period is 7 days (“past week”), and responses are reported using verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale /item represents a high level of symptomatology/problems.
14. Change from baseline in treatment-related symptoms as assessed by patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE), determined from baseline up through to cycle 6. The National Cancer Institute's (NCI's) PRO-CTCAE is an item library of common AEs experienced by people with cancer that are appropriate for self-reporting of treatment tolerability. Each symptom selected for inclusion can be rated by up to 3 attributes characterising the presence/frequency, severity, and/or interference of the AEs. It ranges from 0 to 4 with higher scores indicating higher frequency or greater severity /impact.
15. Change from baseline in symptoms, functioning, and overall HRQoL as assessed by EuroQol five dimension questionnaire 5-level (EQ-5D-5L), determined from baseline up to 11 years. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analogue scale rating “health today” with anchors ranging from 0 (worst imaginable) to 100 (best imaginable health state).
16. Time to sustained worsening in symptoms, functioning and HRQoL, defined as the time interval from the date of randomisation to the start date of meaningful change, measured up to 11 years.

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Original secondary outcome measures:

1. Very good partial response (VGPR) or better, defined as the percentage of participants achieving VGPR and CR (including stringent complete response [sCR]) prior to subsequent antimyeloma therapy in accordance with the International Myeloma Working Group (IMWG) criteria during or after the study treatment, determined up to 9 years.
2. Complete response (CR) or better, defined as the percentage of participants achieving CR or sCR prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment, determined for up to 9 years.

3. MRD-negative CR, defined as the percentage of participants who achieve MRD-negative status, (determined by NGS with a sensitivity of 10^-5) at any time after randomisation and prior to progressive disease or subsequent antimyeloma therapy and who achieve CR or better, determined up to 9 years.
4. Progression-free survival on next-line therapy (PFS2), defined as the time interval between the date of randomisation and the date of the event, which is defined as progressive disease as assessed by the investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first, measured up to 9 years.
5. Overall survival (OS), defined as the time interval from the date of randomisation to the date of death due to any cause, measured up to 9 years.
6. Number of participants with adverse events (AEs) by severity determined up to 9 years. An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product and does not necessarily have a causal relationship with the treatment. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5. Severity scale ranges from Grade 1 mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening, and Grade 5 death related to adverse event.
7. Number of participants with abnormalities in laboratory parameters (serum chemistry and haematology) determined up to 9 years.
8. Number of participants with abnormalities in vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure) determined up to 9 years.
9. Number of participants with abnormalities in physical examination determined up to 9 years.
10. Number of participants with abnormalities in electrocardiogram (ECG) determined up to 9 years.
11. Serum concentrations of Teclistamab measured by validated, specific and sensitive methods up to 9 years.
12. Number of participants with anti-drug antibodies (ADAs) to Teclistamab determined up to 9 years.
13. Change from baseline in symptoms, functioning, and health-related quality of life (HRQoL) as assessed by a European organisation for research and treatment of cancer quality-of-life questionnaire core 30 (EORTC-QLQ-C30) determined from baseline up to 9 years. The EORTC-QLQ-C30 Version 3 includes 30 items that makeup 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea /vomiting), and 5 single symptom items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) and a single impact item (financial difficulties). The recall period is 7 days (“past week”), and responses are reported using verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale /item represents a high level of symptomatology/problems.
14. Change from baseline in treatment-related symptoms as assessed by patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE), determined from baseline up to day 15 of cycle 6. The National Cancer Institute's (NCI's) PRO-CTCAE is an item library of common AEs experienced by people with cancer that are appropriate for self-reporting of treatment tolerability. Each symptom selected for inclusion can be rated by up to 3 attributes characterizing the presence/frequency, severity, and/or interference of the AEs. It ranges from 0 to 4 with higher scores indicating higher frequency or greater severity /impact.
15. Change from baseline in symptoms, functioning, and overall HRQoL as assessed by EuroQol five dimension questionnaire 5-level (EQ-5D-5L), determined from baseline up to 9 years. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analogue scale rating “health

today" with anchors ranging from 0 (worst imaginable) to 100 (best imaginable health state).
16. Time to sustained worsening in symptoms, functioning and HRQoL, defined as the time interval from the date of randomisation to the start date of meaningful change, measured up to 9 years.

Overall study start date
26/10/2021

Completion date
29/08/2033

Eligibility

Key inclusion criteria
Current exclusion criteria as of 30/10/2024:

1. Received any prior therapy for multiple myeloma or smouldering myeloma other than a short course of corticosteroids (not to exceed 40 milligrams [mg] of dexamethasone, or equivalent per day for a maximum of 4 days, a total of 160 mg dexamethasone or equivalent). In addition, received a cumulative dose of systemic corticosteroids equivalent to greater than or equal to (>=)20 mg of dexamethasone within 14 days before randomisation
2. Had plasmapheresis within 28 days of randomisation
3. Had a stroke, transient ischaemic attack, or seizure within 6 months prior to randomisation
4. Known allergies, hypersensitivity, or intolerance to teclistamab or talquetamab excipients
5. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information
6. Myeloma Frailty Index of >=2 with the exception of participants who have a score of 2 based on age alone

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Previous inclusion criteria as of 03/01/2024 30/10/2024:

1. Sex: All
2. Gender-Based: No
3. Aged 18 years old and over
4. Have a diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria
5. Be newly diagnosed and not considered a candidate for high-dose chemotherapy with autologous stem cell transplant (ASCT) due to: ineligible due to advanced age OR; ineligible due to the presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT OR; deferral of high-dose chemotherapy with ASCT as initial treatment
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2
7. A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment
8. A participant must agree not to plan to father a child while enrolled in this study or within 100 days after the last dose of study treatment

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Previous inclusion criteria from 14/09/2023 to 03/01/2024:

1. Sex: All
2. Gender-Based: No
3. Aged 18 years old and over
4. Have a diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria
5. Be newly diagnosed and not considered a candidate for high-dose chemotherapy with autologous stem cell transplant (ASCT) due to: ineligible due to advanced age OR; ineligible due to the presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT OR; deferral of high-dose chemotherapy with ASCT as initial treatment
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2
7. A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment
8. A participant must agree not to plan to father a child while enrolled in this study or within 3 months after the last dose of study treatment.

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Previous inclusion criteria:

1. Sex: All
2. Gender-Based: No
3. Aged 18 years old and over
4. Diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria
5. Be newly diagnosed and not considered a candidate for high-dose chemotherapy with autologous stem cell transplant (ASCT) due to:
5.1. Advanced age OR
5.2. Presence of comorbid condition(s) likely to have a negative impact on the tolerability of high-dose chemotherapy with ASCT OR
5.3. Deferral of high-dose chemotherapy with ASCT as initial treatment
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2
7. A female participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study treatment
8. A male participant must agree not to plan to father a child while enrolled in this study or within 3 months after the last dose of study treatment

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1030

Key exclusion criteria
Current exclusion criteria as of 14/09/2023:

1. Received any prior therapy for multiple myeloma or smouldering myeloma other than a short course of corticosteroids (not to exceed 40 milligrams [mg] of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent). In addition, received a cumulative dose of systemic corticosteroids equivalent to greater than or equals to (>=)20 mg of dexamethasone during the Screening Phase
2. Had plasmapheresis within 28 days of randomisation
3. Had a stroke, transient ischaemic attack, or seizure within 6 months prior to randomisation
4. Known allergies, hypersensitivity, or intolerance to teclistamab or talquetamab excipients
5. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information
6. Myeloma Frailty Index of >=2 with the exception of participants who have a score of 2 based on age alone

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Previous exclusion criteria:

1. Received a cumulative dose of systemic corticosteroids equivalent to greater than or equal to (>=) 20 milligrams (mg) of dexamethasone within 14 days before randomisation
2. Had plasmapheresis within 28 days of randomisation
3. Had a stroke, transient ischemic attack, or seizure within 6 months prior to randomisation
4. Known allergies, hypersensitivity, or intolerance to teclistamab excipients
5. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information

Date of first enrolment
25/10/2022

Date of final enrolment
28/01/2027

Locations

Countries of recruitment
Australia

Austria

Belgium

Brazil

Canada

China

Denmark

France

Germany

Greece

Hungary

India

Italy

Japan

Netherlands

Norway

Poland

Portugal

Spain

Sweden

Türkiye

United Kingdom

Study participating centre
Hammersmith Hospital
Lead UK site
Du Cane Road
Hammersmith
London
United Kingdom
W12 0HS

Sponsor information

Organisation
Janssen-Cilag International NV

Sponsor details

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Leiden
Netherlands
2333 CM
(+31) 71 524 21 06
ClinicalTrialsEU@its.jnj.com

Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
Janssen Research and Development

Alternative Name(s)
Janssen R&D, Janssen Research & Development, Janssen Research & Development, LLC, Janssen Research & Development LLC, Janssen Pharmaceutical Companies of Johnson & Johnson, Research & Development at Janssen, JRD, J&J PRD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Study results will be available via publication in scientific journals, the EudraCT database & presentation at scientific meetings. Results will be made available to participants via a Plain Language Summary a year after the end of the study. The summary will describe the results regardless of the study outcome in language that is understandable to the general public. It will not contain individual participant results or personal information. A copy of the Summary will be provided to the REC.

Intention to publish date
29/08/2034

Individual participant data (IPD) sharing plan

The data sharing policy of the Janssen Pharmaceutical Companies of Johnson and Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at yoda.yale.edu.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No