



Clinical trial results:

A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma

Summary

| | |
|--------------------------|---|
| EudraCT number | 2009-017903-28 |
| Trial protocol | NL IS BE DK AT SE IT CZ SK GR PT FI HU LU |
| Global end of trial date | 18 October 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 11 May 2025 |
| First version publication date | 11 May 2025 |

Trial information

Trial identification

| | |
|-----------------------|------|
| Sponsor protocol code | HO95 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | HOVON |
| Sponsor organisation address | Dr. Molewaterplein 40, Rotterdam, Netherlands, |
| Public contact | HOVON, HOVON, hovon@erasmusmc.nl |
| Scientific contact | HOVON, HOVON, hovon@erasmusmc.nl |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 November 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 October 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To assess the efficacy of VMP versus high-dose therapy and stem cell transplantation (HDT) in patients with previously untreated multiple myeloma, as measured by the progression free survival.
- To evaluate the effect of consolidation with VRD followed by Lenalidomide maintenance with no consolidation but Lenalidomide maintenance alone on progression free survival.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 21 January 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 356 |
| Country: Number of subjects enrolled | Norway: 29 |
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Sweden: 53 |
| Country: Number of subjects enrolled | Austria: 20 |
| Country: Number of subjects enrolled | Belgium: 29 |
| Country: Number of subjects enrolled | Czechia: 80 |
| Country: Number of subjects enrolled | Denmark: 54 |
| Country: Number of subjects enrolled | Greece: 37 |
| Country: Number of subjects enrolled | Iceland: 2 |
| Country: Number of subjects enrolled | Italy: 718 |
| Country: Number of subjects enrolled | Luxembourg: 1 |
| Country: Number of subjects enrolled | Australia: 17 |
| Country: Number of subjects enrolled | Türkiye: 60 |
| Country: Number of subjects enrolled | Switzerland: 42 |
| Worldwide total number of subjects | 1503 |
| EEA total number of subjects | 1384 |

Notes:

| Subjects enrolled per age group | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1417 |
| From 65 to 84 years | 86 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects gave written informed consent and were screened according to the inclusion- and exclusion criteria

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|--|---------------|
| Arm title | Experimental |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | lenalidomide |
| Investigational medicinal product code | |
| Other name | REVLIMID® |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

The recommendations for initial starting doses of REVLIMID® for patients with MM are as follows while maintaining a 21 out of 28 day treatment cycle:

Renal Function (CrCL) | Multiple Myeloma Dose

Mild Renal Impairment ($90 > \text{CrCL} \geq 60 \text{ mL/min}$) | 25 mg (Normal Dose) Every 24 hours

Moderate Renal Impairment ($30 \leq \text{CrCL} < 60 \text{ mL/min}$) | 10 mg Every 24 hours

Severe Renal Impairment ($\text{CrCL} < 30 \text{ mL/min}$, not requiring dialysis) | 15 mg Every 48 hours

End Stage Renal Disease ($\text{CrCL} < 30 \text{ mL/min}$, requiring dialysis) | 5 mg Once daily. On dialysis days the dose should be administered following dialysis

The dose may be escalated to 15 mg every 24 hours after 2 cycles if patient is not responding to treatment and is tolerating the drug.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | |
| Other name | VELCADE |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

The recommended starting dose of bortezomib is 1.3 mg/m² body surface area twice a week for two weeks (administration on days 1, 4, 8 and 11), followed by a 10-day rest period (days 12-21). This three-week period is considered one treatment cycle. There must be at least 72 hours between successive doses of VELCADE. It is recommended that patients with proven complete remission be treated with 2 additional VELCADE cycles after establishing complete remission. It is also recommended that responding patients who do not achieve complete remission be treated with a total of 8 VELCADE cycles. Few data are currently available on re-treatment with VELCADE.

| Number of subjects in period 1 | Experimental |
|---------------------------------------|--------------|
| Started | 1503 |
| Completed | 0 |
| Not completed | 1503 |
| Consent withdrawn by subject | 68 |
| Adverse event, non-fatal | 309 |
| Other | 424 |
| Unknown (Early consent withdrawal) | 3 |
| Lack of efficacy | 699 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Overall period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values | Overall period | Total | |
|------------------------|----------------|-------|--|
| Number of subjects | 1503 | 1503 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 1417 | 1417 | |
| Adults (65 years) | 86 | 86 | |
| Age continuous | | | |
| Units: years | | | |
| median | 58 | | |
| full range (min-max) | 28 to 66 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 634 | 634 | |
| Male | 869 | 869 | |

End points

End points reporting groups

| | |
|--------------------------------|--------------|
| Reporting group title | Experimental |
| Reporting group description: - | |

Primary: Primary endpoint

| | |
|------------------------|---------------------------------|
| End point title | Primary endpoint ^[1] |
| End point description: | |

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

See publication

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached chart/documents for results

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Experimental | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1503 | | | |
| Units: Whole | 1503 | | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Statistical data section from publication/Methods+results.pdf List of reported SAEs/saedata95-25Nov2024.pdf List of reported non-SAEs/nonsaedata95-25Nov2024.pdf |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | v4 |

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Experimental group |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Experimental group | | |
|---|----------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 714 / 1493 (47.82%) | | |
| number of deaths (all causes) | 686 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm benign, malignant and unspecif. (inc. cysts/polyp) | Additional description: combined | | |
| subjects affected / exposed | 101 / 1493 (6.76%) | | |
| occurrences causally related to treatment / all | 75 / 113 | | |
| deaths causally related to treatment / all | 6 / 12 | | |
| Vascular disorders | | | |
| Vascular disorders | Additional description: combined | | |
| subjects affected / exposed | 39 / 1493 (2.61%) | | |
| occurrences causally related to treatment / all | 23 / 41 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Surgical and medical procedures | | | |
| Surgical and medical procedures | Additional description: combined | | |
| subjects affected / exposed | 12 / 1493 (0.80%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|----------------------------------|--|--|
| General disorders and administration site conditions | Additional description: combined | | |
| subjects affected / exposed | 164 / 1493 (10.98%) | | |
| occurrences causally related to treatment / all | 90 / 218 | | |
| deaths causally related to treatment / all | 5 / 26 | | |
| Immune system disorders | | | |
| Immune system disorders | Additional description: Combined | | |
| subjects affected / exposed | 7 / 1493 (0.47%) | | |
| occurrences causally related to treatment / all | 4 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Reproductive system and breast disorders | | | |
| Reproductive system and breast disorders | Additional description: combined | | |
| subjects affected / exposed | 4 / 1493 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory, thoracic and mediastinal disorders | Additional description: combined | | |
| subjects affected / exposed | 75 / 1493 (5.02%) | | |
| occurrences causally related to treatment / all | 50 / 85 | | |
| deaths causally related to treatment / all | 3 / 16 | | |
| Psychiatric disorders | | | |
| Psychiatric disorders | Additional description: combined | | |
| subjects affected / exposed | 12 / 1493 (0.80%) | | |
| occurrences causally related to treatment / all | 7 / 12 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Investigations | | | |
| Investigations | Additional description: combined | | |
| subjects affected / exposed | 17 / 1493 (1.14%) | | |
| occurrences causally related to treatment / all | 22 / 24 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Injury, poisoning and procedural complications | Additional description: combined | | |

| | | | |
|---|----------------------------------|--|--|
| subjects affected / exposed | 32 / 1493 (2.14%) | | |
| occurrences causally related to treatment / all | 3 / 32 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Congenital, familial and genetic disorders | | | |
| Congenital, familial and genetic disorders | Additional description: Combined | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac disorders | Additional description: Combined | | |
| subjects affected / exposed | 33 / 1493 (2.21%) | | |
| occurrences causally related to treatment / all | 17 / 33 | | |
| deaths causally related to treatment / all | 1 / 5 | | |
| Nervous system disorders | | | |
| Nervous system disorder | Additional description: combined | | |
| subjects affected / exposed | 67 / 1493 (4.49%) | | |
| occurrences causally related to treatment / all | 29 / 79 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Blood and lymphatic system disorders | | | |
| Blood and lymphatic system disorders | Additional description: Combined | | |
| subjects affected / exposed | 52 / 1493 (3.48%) | | |
| occurrences causally related to treatment / all | 38 / 53 | | |
| deaths causally related to treatment / all | 2 / 7 | | |
| Eye disorders | | | |
| Eye disorders | Additional description: Combined | | |
| subjects affected / exposed | 5 / 1493 (0.33%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | Additional description: combined | | |
| subjects affected / exposed | 97 / 1493 (6.50%) | | |
| occurrences causally related to treatment / all | 59 / 107 | | |
| deaths causally related to treatment / all | 2 / 7 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------------------------|--|--|
| Hepatobiliary disorders | Additional description: Combined | | |
| subjects affected / exposed | 14 / 1493 (0.94%) | | |
| occurrences causally related to treatment / all | 3 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | Additional description: combined | | |
| Skin and subcutaneous tissue disorders | Additional description: combined | | |
| subjects affected / exposed | 16 / 1493 (1.07%) | | |
| occurrences causally related to treatment / all | 9 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | Additional description: combined | | |
| Renal and urinary disorders | Additional description: combined | | |
| subjects affected / exposed | 25 / 1493 (1.67%) | | |
| occurrences causally related to treatment / all | 12 / 25 | | |
| deaths causally related to treatment / all | 2 / 5 | | |
| Endocrine disorders | Additional description: Combined | | |
| Endocrine disorders | Additional description: Combined | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | Additional description: combined | | |
| Musculoskeletal and connective tissue disorders | Additional description: combined | | |
| subjects affected / exposed | 45 / 1493 (3.01%) | | |
| occurrences causally related to treatment / all | 7 / 48 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | Additional description: combined | | |
| Infections and infestations | Additional description: combined | | |
| subjects affected / exposed | 240 / 1493 (16.08%) | | |
| occurrences causally related to treatment / all | 186 / 329 | | |
| deaths causally related to treatment / all | 5 / 13 | | |
| Metabolism and nutrition disorders | Additional description: combined | | |
| Metabolism and nutrition disorders | Additional description: combined | | |
| subjects affected / exposed | 32 / 1493 (2.14%) | | |
| occurrences causally related to treatment / all | 14 / 32 | | |
| deaths causally related to treatment / all | 1 / 1 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| | | | |
|---|----------------------------------|--|--|
| Non-serious adverse events | Experimental group | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1436 / 1493 (96.18%) | | |
| Injury, poisoning and procedural complications | | | |
| Other toxicity | Additional description: Combined | | |
| subjects affected / exposed | 678 / 1493 (45.41%) | | |
| occurrences (all) | 1335 | | |
| Vascular disorders | | | |
| Vascular disorders | Additional description: Combined | | |
| subjects affected / exposed | 193 / 1493 (12.93%) | | |
| occurrences (all) | 279 | | |
| Cardiac disorders | | | |
| Cardiac disorders | Additional description: Combined | | |
| subjects affected / exposed | 111 / 1493 (7.43%) | | |
| occurrences (all) | 143 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | Additional description: Combined | | |
| subjects affected / exposed | 941 / 1493 (63.03%) | | |
| occurrences (all) | 2563 | | |
| Neutropenia | Additional description: Combined | | |
| subjects affected / exposed | 978 / 1493 (65.51%) | | |
| occurrences (all) | 2290 | | |
| Thrombocytopenia | Additional description: Combined | | |
| subjects affected / exposed | 913 / 1493 (61.15%) | | |
| occurrences (all) | 2053 | | |
| Gastrointestinal disorders | | | |
| GI & Hepatic disorders | Additional description: Combined | | |
| subjects affected / exposed | 891 / 1493 (59.68%) | | |
| occurrences (all) | 1727 | | |

| | | | |
|---|----------------------------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Respir, thor, medias disorders | Additional description: Combined | | |
| subjects affected / exposed | 299 / 1493 (20.03%) | | |
| occurrences (all) | 353 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin & subcutaneous disorders | Additional description: Combined | | |
| subjects affected / exposed | 482 / 1493 (32.28%) | | |
| occurrences (all) | 716 | | |
| Renal and urinary disorders | | | |
| Renal & urin. disorders | Additional description: Combined | | |
| subjects affected / exposed | 102 / 1493 (6.83%) | | |
| occurrences (all) | 121 | | |
| Infections and infestations | | | |
| Infection & Febrile neut | Additional description: Combined | | |
| subjects affected / exposed | 666 / 1493 (44.61%) | | |
| occurrences (all) | 998 | | |
| Metabolism and nutrition disorders | | | |
| Invest. & metab. disorders | Additional description: Combined | | |
| subjects affected / exposed | 452 / 1493 (30.27%) | | |
| occurrences (all) | 869 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 28 June 2011 | AM 1 Italy |
| 03 January 2012 | AM 2 The change(s) in this amendment relates to the addition of ROD2 JIT label Lenalidomide. |
| 26 March 2012 | AM 1 nordic |
| 30 November 2012 | AM 3 addition Quality of life substudy - addition Iron deficiency substudy - addition substudy Evaluation PET scan in young MM patients - duration of follow-up period - criteria measurable disease - modification schedule VCD induction - addition dose adjustments during VCD, VMP and VRD treatment - change in information molecular substudies - addition reporting of Second Primary Malignancies |
| 13 May 2013 | AM 4 (protocol v5) The changes in this amendment relate to - removing the 7.5mg and 2.5mg doses of Lenalidomide for dose reduction during the VRD course in case of toxicities - changing the dose reduction schedule of Cyclophosphamide during VCD (removal day 15). |

| | |
|------------------|---|
| 12 March 2014 | <p>AM5 (= protocol v 6)</p> <p>change in the duration of a course of Lenalidomide maintenance treatment from 28 days to 21 days</p> <p>change in eligibility criteria of stem cell mobilization</p> <p>clarification of the timelines of randomization relative to the start of VRD/maintenance treatment</p> <p>addition of FISH analysis at progression</p> <p>correction response evaluation</p> <p>clarification of precautions during Bortezomib treatment and Lenalidomide maintenance treatment</p> <p>clarification of dose adjustments of Bortezomib</p> <p>addition of the possibility of crossover from the VMP arm to the HDM arm in case of Bortezomib toxicity during VMP</p> <p>clarification of timelines of bone marrow punctures and response evaluations</p> <p>addition of additional information about the MRD substudy</p> <p>addition of side effects of Bortezomib</p> <p>correction dose of cyclophosphamide and CRAB criteria</p> <p>change local investigator in specified sites</p> |
| 28 November 2014 | AM06 Switzerland |
| 06 May 2019 | <p>AM07 (Brexit preparations)</p> <p>Change in marketing authorization holder</p> <p>Addition of EU IMP release site</p> |
| 12 February 2020 | <p>AM08 (= protocol v 7)</p> <p>-Lenalidomide maintenance treatment is given until progression of disease (previously until relapse/progression)</p> <p>-All patients are followed up to 10 years after registration instead of 7 years</p> <p>- Administrative changes</p> |
| 02 July 2021 | <p>AM09 (= protocol v 8)</p> <p>Lenalidomide maintenance treatment is given as an investigational treatment for 10 years. Patients who continue to benefit from this treatment after 10 years continue their maintenance regimens outside of study settings. - - -</p> <p>Additional patient information letter</p> <p>Change of local investigator or independent physician</p> <p>Merger/renaming of hospitals</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34774221>