



Clinical trial results:

A randomized phase II multicenter study to assess the tolerability and efficacy of the addition of ibrutinib to 10-day decitabine in UNFIT (i.e. HCT-CI 3) AML and high risk myelodysplasia (MDS) (IPSS-R > 4.5) patients aged ≥66 years.

A study in the frame of the masterprotocol of parallel randomized phase II studies in UNFIT-older AML/high-risk MDS patients.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002855-85 |
| Trial protocol | NL BE LT |
| Global end of trial date | 10 July 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 08 June 2025 |
| First version publication date | 08 June 2025 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | HO135 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | METC UMCG: 2015.550, Nederlands Trialregister: NTR6017, CCMO dossiernr: NL55164.042.15 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | HOVON |
| Sponsor organisation address | Dr. Molewaterplein 40, Rotterdam, Netherlands, |
| Public contact | HOVON Data Center, HOVON, hdc@erasmusmc.nl |
| Scientific contact | HOVON Data Center, HOVON, hdc@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 | 18 February 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 July 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To assess in a randomized comparison the effect of ibrutinib added to 10-day decitabine treatment on the cumulative CR/CRi rate after 3 cycles.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 07 September 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 85 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Lithuania: 10 |
| Country: Number of subjects enrolled | Switzerland: 40 |
| Worldwide total number of subjects | 148 |
| EEA total number of subjects | 108 |

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) | 0 |

| | |
|---------------------|-----|
| From 65 to 84 years | 144 |
| 85 years and over | 4 |

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

| | |
|--|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Experimental |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | decitabine |
| Investigational medicinal product code | |
| Other name | DACOGEN |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The 5-Day dosing regimen is defined as 20 mg/m² DACOGEN administered as a 1 hour IV infusion for 5 consecutive days every 4weeks. The 3-Day dosing regimen is defined as 15 mg/m² DACOGEN administered as a 3 hour IV infusion every 8 hours for 3 consecutive days every 6 weeks

| | |
|--|-----------------------|
| Investigational medicinal product name | Ibrutinib |
| Investigational medicinal product code | |
| Other name | IMBRUVICA |
| Pharmaceutical forms | Capsule, hard, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The recommended dose of ibrutinib for MCL or MZL is 560 mg orally once daily until disease progression or no longer tolerated by the subject.

| | |
|--|-----------------------------------|
| Arm title | Control |
| Arm description: | |
| Standard of care; Decatibine | |
| Arm type | Active comparator |
| Investigational medicinal product name | decitabine |
| Investigational medicinal product code | |
| Other name | DACOGEN |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The 5-Day dosing regimen is defined as 20 mg/m² DACOGEN administered as a 1 hour IV infusion for 5 consecutive days every 4weeks. The 3-Day dosing regimen is defined as 15 mg/m² DACOGEN administered as a 3 hour IV infusion every 8 hours for 3 consecutive days every 6 weeks

| Number of subjects in period 1 | Experimental | Control |
|---------------------------------------|--------------|---------|
| Started | 74 | 74 |
| Completed | 0 | 0 |
| Not completed | 74 | 74 |
| Adverse reactions | 14 | 7 |
| Other | 7 | 11 |
| At patient's request | 13 | 6 |
| Lack of efficacy | 40 | 50 |

Baseline characteristics

Reporting groups

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

Reporting group description: -

| Reporting group values | Overall period | Total | |
|---|----------------|-------|--|
| Number of subjects | 148 | 148 | |
| Age categorical | | | |
| Previously untreated adults who were ≥ 66 years old and not considered eligible for intensive chemotherapy, with a cytopathologically confirmed diagnosis of AML or with higher risk MDS (Revised International Prognostic Scoring System score .4.5), a World Health Organization (WHO) performance status #2, and written informed consent, were eligible. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 144 | 144 | |
| 85 years and over | 4 | 4 | |
| Age continuous | | | |
| Units: years | | | |
| median | 76 | | |
| full range (min-max) | 66 to 89 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 56 | 56 | |
| Male | 92 | 92 | |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Experimental |
| Reporting group description: - | |
| Reporting group title | Control |
| Reporting group description: Standard of care; Decatibine | |

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 | Control | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 74 | | |
| Units: Whole | 74 | 74 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | HO135_Statistical data section from publication_22MAY2025. nonsaedata135-22May2025.pdf saedata135-22May2025.pdf |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events 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, if earlier.

Adverse event reporting additional description:

Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the local investigator.

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

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Control group |
|-----------------------|---------------|

Reporting group description: -

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

Reporting group description:

Actual number of deaths all causes is 72. Patient died after randomization but before starting treatment.

| Serious adverse events | Control group | Experimental group | |
|---|---|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 59 / 73 (80.82%) | 65 / 71 (91.55%) | |
| number of deaths (all causes) | 70 | 71 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 6 / 73 (8.22%) | 6 / 71 (8.45%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Vascular disorders | | | |
| Vascular disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General disorders and administration site conditions | Additional description: All combined, see non-SAE chart for details | | |

| | | | |
|---|---|-----------------|--|
| subjects affected / exposed | 5 / 73 (6.85%) | 8 / 71 (11.27%) | |
| occurrences causally related to treatment / all | 4 / 7 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Immune system disorders | | | |
| Immune system disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Reproductive system and breast disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory, thoracic and mediastinal disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 6 / 73 (8.22%) | 6 / 71 (8.45%) | |
| occurrences causally related to treatment / all | 4 / 8 | 2 / 6 | |
| deaths causally related to treatment / all | 2 / 4 | 0 / 0 | |
| Psychiatric disorders | | | |
| Psychiatric disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Investigations | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injury, poisoning and procedural complications | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 2 / 73 (2.74%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|------------------|--|
| Cardiac disorders | | | |
| Cardiac disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 6 / 73 (8.22%) | 6 / 71 (8.45%) | |
| occurrences causally related to treatment / all | 2 / 6 | 4 / 6 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Nervous system disorders | | | |
| Nervous system disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 7 / 73 (9.59%) | 3 / 71 (4.23%) | |
| occurrences causally related to treatment / all | 4 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Blood and lymphatic system disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 21 / 73 (28.77%) | 23 / 71 (32.39%) | |
| occurrences causally related to treatment / all | 29 / 32 | 24 / 30 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 7 / 73 (9.59%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 1 / 7 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and subcutaneous tissue disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|------------------|--|
| Renal and urinary disorders | | | |
| Renal and urinary disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 2 / 73 (2.74%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Endocrine disorders | | | |
| Endocrine disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal and connective tissue disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infections and infestations | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 35 / 73 (47.95%) | 35 / 71 (49.30%) | |
| occurrences causally related to treatment / all | 32 / 48 | 22 / 48 | |
| deaths causally related to treatment / all | 7 / 10 | 6 / 9 | |

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

| Non-serious adverse events | Control group | Experimental group | |
|---|---|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 73 (87.67%) | 66 / 71 (92.96%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 71 (1.41%) | |
| occurrences (all) | 1 | 1 | |
| Vascular disorders | | | |
| Vascular disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed | 15 / 73 (20.55%) | 12 / 71 (16.90%) | |
| occurrences (all) | 15 | 14 | |
| Surgical and medical procedures | | | |

| | | | |
|--|---|------------------------|--|
| Surgical and medical procedures subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 2 / 73 (2.74%) 2 | 0 / 71 (0.00%) 0 | |
| General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 18 / 73 (24.66%) 21 | 18 / 71 (25.35%) 24 | |
| Immune system disorders Immune system disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 2 / 73 (2.74%) 2 | 1 / 71 (1.41%) 1 | |
| Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 0 / 73 (0.00%) 0 | 1 / 71 (1.41%) 1 | |
| Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 10 / 73 (13.70%) 12 | 12 / 71 (16.90%) 14 | |
| Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 3 / 73 (4.11%) 4 | 4 / 71 (5.63%) 6 | |
| Investigations Investigations subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 20 / 73 (27.40%) 41 | 16 / 71 (22.54%) 27 | |
| Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 1 / 73 (1.37%) 1 | 5 / 71 (7.04%) 5 | |
| Cardiac disorders Cardiac disorders | Additional description: All combined, see non-SAE chart for details | | |
| | | | |

| | | | |
|--|---|------------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 73 (13.70%) 12 | 14 / 71 (19.72%) 17 | |
| Nervous system disorders | | | |
| Nervous system disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 7 / 73 (9.59%) 10 | 9 / 71 (12.68%) 11 | |
| Blood and lymphatic system disorders | | | |
| Blood and lymphatic system disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 13 / 73 (17.81%) 14 | 18 / 71 (25.35%) 22 | |
| Ear and labyrinth disorders | | | |
| Ear and labyrinth disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 2 / 71 (2.82%) 2 | |
| Eye disorders | | | |
| Eye disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 4 / 73 (5.48%) 4 | 0 / 71 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 24 / 73 (32.88%) 33 | 25 / 71 (35.21%) 39 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 0 / 73 (0.00%) 0 | 2 / 71 (2.82%) 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and subcutaneous tissue disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 8 / 73 (10.96%) 8 | 14 / 71 (19.72%) 16 | |
| Renal and urinary disorders | | | |
| Renal and urinary disorders | Additional description: All combined, see non-SAE chart for details | | |
| subjects affected / exposed occurrences (all) | 5 / 73 (6.85%) 5 | 6 / 71 (8.45%) 6 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|---|------------------|--|
| Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 10 / 73 (13.70%) | 4 / 71 (5.63%) | |
| | 12 | 4 | |
| Infections and infestations Infections and infestations subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 37 / 73 (50.68%) | 34 / 71 (47.89%) | |
| | 58 | 51 | |
| Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all) | Additional description: All combined, see non-SAE chart for details | | |
| | 13 / 73 (17.81%) | 16 / 71 (22.54%) | |
| | 21 | 34 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 07 February 2017 | It involves adding a new centers: Isala Clinic, Zwolle OLVG, Amsterdam Reinier de graaf groep, Delft |
| 22 April 2022 | It involves a change of investigators in the following hospitals: Meander MC, Amersfoort MUMC, Maastricht Rijnstate, Arnhem |

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/32915972>