

**Clinical trial results:****THE EFFICACY AND SAFETY OF LENALIDOMIDE (Revlimid®)
MONOTHERAPY IN RED BLOOD CELL TRANSFUSION DEPENDENT
SUBJECTS WITH MYELODYSPLASTIC SYNDROME ASSOCIATED WITH
A DEL (5q) CYTOGENETIC ABNORMALITY****Summary**

| | |
|--------------------------|----------------|
| EudraCT number | 2004-005101-29 |
| Trial protocol | GB |
| Global end of trial date | 23 May 2016 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 21 September 2019 |
| First version publication date | 21 September 2019 |
| Summary attachment (see zip file) | RESULTS SUMMARY (revlimid results summary.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------------|
| Sponsor protocol code | KCH-MDS-04-1.0 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00874978 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | King's College Hospital |
| Sponsor organisation address | Denmark Hill , London, United Kingdom, SE5 9RS |
| Public contact | Professor Ghulam Mufti, King's College Hospital NHS Foundation Trust, 0044 0203299 3080, ghulam.mufti@kcl.ac.uk |
| Scientific contact | Professor Ghulam Mufti, King's College Hospital NHS Foundation Trust, 0044 0203299 3080, ghulam.mufti@kcl.ac.uk |
| Sponsor organisation name | King's College London |
| Sponsor organisation address | Strand, London, United Kingdom, WC2R 2LS |
| Public contact | Professor Ghulam Mufti, King's College London, 0044 02032993080, ghulam.mufti@kcl.ac.uk |
| Scientific contact | Professor Ghulam Mufti, King's College London, 0044 02032993080, ghulam.mufti@kcl.ac.uk |

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 | 23 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 May 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk International Prognostic Scoring System1 (IPSS) myelodysplastic syndrome (MDS) associated with a del 5q cytogenetic abnormality
 To evaluate the efficacy of lenalidomide to achieve haematopoietic improvement in patients with isolated del5q with blasts <20%

Protection of trial subjects:

Forty eight (48) subjects with a diagnosis of low- or intermediate-1 risk MDS associated with a del 5(q) cytogenetic abnormality or isolated del5(q) patients with up to 20% blasts, who are RBC transfusion-dependent and meet all the eligibility criteria will be enrolled into the study

Background therapy:

None

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 03 January 2005 |
| 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 | United Kingdom: 44 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 44 |

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) | 23 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical site in the UK between 2005 and 2016

Pre-assignment

Screening details:

Aged 18 or over with diagnosis of low- or intermediate-1-risk (IPSS) MDS with a del(5q) cytogenetic abnormality which may be an isolated finding or may be associated with other cytogenetic abnormalities & if del5(q) is an isolated aberration the patient could have up to 20% blasts

Period 1

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

Blinding implementation details:

This study is a single centre, single-arm, open-label study of oral lenalidomide monotherapy administered to red blood cell (RBC) transfusion dependent subjects with IPSS low- or intermediate-1 risk MDS associated with a del5(q) cytogenetic abnormality and also in patients with isolated del5q with blasts <20%.

Arms

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

Dosage and administration details:

Oral lenalidomide 10mg (two 5mg capsules) daily on Days 1-21 every 28 days for up to 12 cycles or until bone marrow disease progression or progression/relapse following erythroid haematologic improvement (Appendix 2). At the end of 12 cycles, if there is erythroid haematologic improvement, subjects will receive further cycles until bone marrow disease progression or progression/relapse.

| Number of subjects in period 1 | Overall Trial |
|---------------------------------------|---------------|
| Started | 44 |
| Completed | 36 |
| Not completed | 8 |
| Adverse event, serious fatal | 8 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---------------------------------------|---------------|-------|--|
| Number of subjects | 44 | 44 | |
| Age categorical Units: Subjects | | | |
| Adults (18-70 years) | 25 | 25 | |
| Adults (71-80years) | 15 | 15 | |
| 81 years and over | 4 | 4 | |
| Gender categorical Units: Subjects | | | |
| Female | 29 | 29 | |
| Male | 15 | 15 | |

End points

End points reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

Primary: Primary

| | |
|-----------------|------------------------|
| End point title | Primary ^[1] |
|-----------------|------------------------|

End point description:

To evaluate the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk International Prognostic Scoring System^[1] (IPSS) myelodysplastic syndrome (MDS) associated with a del 5(q) cytogenetic abnormality.

To evaluate the efficacy of lenalidomide to achieve haematopoietic improvement in patients with isolated del5q with blasts <20%

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

End point timeframe:

During 12 cycles of treatment (12 months). Each cycle lasts 28 days.

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: Please see attached document.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Overall Trial | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: Whole | 36 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary

| | |
|-----------------|-----------|
| End point title | Secondary |
|-----------------|-----------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through 12 cycles of treatment with Revlimid. (each cycle lasting 28 days).

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Overall Trial | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: Whole | 36 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days + 2 days after last IMP dose

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Overall Trial | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 44 (40.91%) | | |
| number of deaths (all causes) | 8 | | |
| number of deaths resulting from adverse events | 8 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma hand | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Irreguglar pulse requiring pacemaker | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myopericarditis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MDS disease progression | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower back pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of appetite | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Left knee pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal disorders | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Peri-anal abscess | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary Embolis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bilateral pleural effusions | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |

| | | | |
|---|----------------|--|--|
| Chest Infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infective exacerbation of COPD | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest sepsis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin rash | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal swelling | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Localised infection & disease progression | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Sepsis - (<i>Stenotrophomonas maltophilia</i>) | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Finger infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Localized infection of hand and elbow | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Overall Trial | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 44 (84.09%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 3 | | |
| Cardiac disorders | | | |
| Heart failure | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | | |
| occurrences (all) | 6 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 44 (29.55%) | | |
| occurrences (all) | 15 | | |
| Headache | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 6 | | |
| Eye disorders Eye infection subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dental Infection subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) | 5 / 44 (11.36%) 6 16 / 44 (36.36%) 30 8 / 44 (18.18%) 11 6 / 44 (13.64%) 7 5 / 44 (11.36%) 5 1 / 44 (2.27%) 1 1 / 44 (2.27%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Chest infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Shortness of breath | 5 / 44 (11.36%) 14 17 / 44 (38.64%) 24 | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed occurrences (all)</p> <p>Epistaxis subjects affected / exposed occurrences (all)</p> | <p>5 / 44 (11.36%) 7</p> <p>1 / 44 (2.27%) 3</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash subjects affected / exposed occurrences (all)</p> <p>Dry skin subjects affected / exposed occurrences (all)</p> <p>Cellulitis subjects affected / exposed occurrences (all)</p> | <p>20 / 44 (45.45%) 35</p> <p>8 / 44 (18.18%) 11</p> <p>1 / 44 (2.27%) 2</p> | | |
| <p>Renal and urinary disorders</p> <p>Urine infection subjects affected / exposed occurrences (all)</p> | <p>3 / 44 (6.82%) 4</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthritis subjects affected / exposed occurrences (all)</p> <p>Neck pain subjects affected / exposed occurrences (all)</p> | <p>2 / 44 (4.55%) 5</p> <p>3 / 44 (6.82%) 3</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 21 April 2010 | <ol style="list-style-type: none">1) Clarification of co-sponsor arrangements between King's College Hospital NHS Foundation Trust and King's College London .2) The investigational medicinal product, lenalidomide, supply beyond the 12 month study phase until patients show disease progression, toxicity or a decline in response.3) The sensitivity and time points for conducting the pregnancy tests and the birth control section altered in line with Celgene's most recent Pregnancy Prevention Programme for Investigator Initiated Trials in the European Union.4) Follow up for patients who discontinue from study drug clarified in the protocol.5) Change of Revlimid status from unlicensed product to confirmation of market authorisation. |
| 19 September 2012 | <ol style="list-style-type: none">1) Change to the inclusion criteria to include patients with MDS and isolated del5q with blasts <20%.2) Changes to the primary and secondary endpoints and study design in relation to the inclusion of patients with isolated del5q with blasts <20%.3) Change in sample size from 36 to 48 patients <p>The protocol has been updated to reflect the changes mentioned above with further administrative changes. The administrative changes include an update to the protocol appendix 4 Pregnancy Testing Guidelines and Acceptable Birth Control Methods, change in department name from Joint Clinical Trials Office to King's Health Partners Clinical Trials Office and change in the address for Celgene.</p> |
| 29 July 2013 | <ol style="list-style-type: none">1) Change in the packaging of the IMP from bottled supply to blister pack2) Change in the site where QP certified batch release |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported