Idasanutlin in addition to cytarabine for relapsed or refractory acute myeloid leukaemia

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<thead>
<tr>
<th>NIHRO ID</th>
<th>NICE ID</th>
<th>Developer/Company</th>
<th>UKPS ID</th>
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<tbody>
<tr>
<td>11985</td>
<td>9763</td>
<td>Roche Products Ltd</td>
<td>645121</td>
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**SUMMARY**

Idasanutlin in addition to cytarabine is in development for the treatment of relapse or refractory Acute Myeloid Leukaemia (AML). AML is a type of cancer that causes the bone marrow (the soft inner part of the bones where new blood cells are made) to produce excess immature white blood cells. The term acute means that it can develop fairly quickly and becomes increasingly more severe. If left untreated it would cause death within a few weeks or months. It is most common in people aged 60 years and over. Symptoms of AML may include weakness, fatigue, shortness of breath, recurrent infections, prolonged bleeding and unintended weight loss. Some risk factors, such as exposure to radiation, smoking, exposure to benzene, cancer treatments or blood or genetic disorders, may increase a person’s risk of developing AML.

The most common treatment option for AML is chemotherapy to kill the cancerous cells. Idasanutlin in addition to cytarabine is a new treatment option that has shown promising clinical activity in acute leukaemia. Idasanutlin acts by blocking the activity of a protein known as MDM2 that is frequently found in AML. Blocking the activity of MDM2 can result in promoting cancer cells death. Idasanutlin is taken orally. If licenced, idasanutlin in addition to cytarabine would offer a new treatment option for patients with relapsed or refractory AML.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
**PROPOSED INDICATION**

Relapsed or refractory acute myeloid leukaemia (AML).\(^a\)

**TECHNOLOGY**

**DESCRIPTION**

Idasanutlin (RG7388) is a second-generation, nutlin-class, orally bioavailable, selective mouse double minute 2 homolog (MDM2) antagonist. MDM2 is an important negative regulator of the p53 tumour suppressor and is expressed at high levels in a large proportion of AML.\(^1\) Idasanutlin exhibits single-nanomolar binding affinity for MDM2 and an average half maximal inhibitory concentration (IC\(_{50}\)) of 40 nM in antiproliferative cell-based assays among wild-type p53 cancer lines.\(^2\) Wild-type p53 is expressed in over 80% of AML cases; thus, inhibition of the interaction between MDM2 and p53 can re-establish the p53 pathway in AML cells resulting in cell cycle arrest and induction of apoptosis.\(^1\)

Idasanutlin is in clinical development for patients with refractory or relapsed AML.\(^3\) In the phase III clinical trial (MIRROS; NCT02545283), idasanutlin is administered orally at a dose of 300mg twice daily (in cycle 1) or once daily (in cycles 2 and 3) in addition to intravenous (IV) infusion of cytarabine, 1 gram per square meter (g/m\(^2\)) for five days of every treatment cycle (treatment cycle length is 28 days).\(^3\)

**INNOVATION AND/OR ADVANTAGES**

Idasanutlin has shown promising clinical activity in acute leukaemias by enhancing the activity of the tumour suppressor, p53, through antagonism of MDM2. In combination with different anticancer drugs, it showed synergism in cancer cellular lines.\(^4,5\) The results from phase 1/1b study evaluating idasanutlin (as monotherapy or in combination with cytarabine) in relapsed or refractory AML patients showed that the MDM2 protein expression in leukemic blasts and stem cells are associated with idasanutlin-induced complete remission in patients with AML.\(^5\)

**DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS**

Idasanutlin does not currently have Marketing Authorisation in the EU/UK for any indication. Idasanutlin is in phase II clinical development for:

- Non-Hodgkin Lymphoma
- Follicular Lymphoma
- Polycythemia Vera

Idasanutlin was granted an orphan designation in the EU in August 2014 for the treatment of acute myeloid leukaemia.\(^7\)

**PATIENT GROUP**

**DISEASE BACKGROUND**

\(^a\) Information provided by Roche Products Ltd.
Leukaemia is cancer of the white blood cells. Acute myeloid leukaemia (AML) refers to a group of blood and bone marrow cancers. This disorder is characterised by incomplete maturation of blood cells and reduced production of other normal haematopoietic stem cells.\textsuperscript{8}

In AML, blood cancer starts mainly from young white blood cells called granulocytes or monocytes. In less common types of AML, too many immature platelets or immature red blood cells are produced. The word acute means that the leukaemia can develop fairly quickly. The leukaemic cells can eventually spread to other parts of the body including the lymph nodes and the spleen.\textsuperscript{8,9}

The causes of AML are unknown and in most cases it is unclear why leukaemia develops. However, there are a number of risk factors that may increase a person’s risk of developing AML, such as exposure to radiation, smoking, exposure to benzene, cancer treatments, blood or genetic disorders.

Most symptoms of AML are due to the effects of the leukaemia cells in the bone marrow and include looking very pale and feeling very tired, becoming breathless easily, having various infections in a short period of time, unusual bleeding and blood spots or rashes on the skin.\textsuperscript{10}

In patients younger than 60 years, treatment of AML typically consists of cytotoxic chemotherapy with a general cure rate of 35–40% depending on the cytogenetic classification while similar outcome can be observed in only 5–15% of older patients, primarily because of their inability to tolerate intensive treatment and their generally higher risk disease features.\textsuperscript{11}

Treatment outcomes in older patients who are unable to receive intensive chemotherapy are extremely poor, with a median survival of 5–10 months. For the majority of treated AML patients who achieve remission, relapse will occur within 3 years of the initial diagnosis. Hence, the prognosis for AML patients following disease relapse is poor and the treatment options are unsatisfactory.\textsuperscript{11}

**CLINICAL NEED AND BURDEN OF DISEASE**

European age standardised incidence rates of AML in England and Wales in 2015 were 5.3 and 5.4 per 100,000 respectively and accounts for less than 1% of all new cancer cases in the UK.\textsuperscript{12}

In England in 2016, there were 3,715 registrations of newly diagnosed cases of myeloid leukaemia (ICD 10 code C92).\textsuperscript{13} AML incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK, the peak rate of AML cases is 85–89 years of age (based on 2013-2015 data). In the UK, 56% of AML cases are in males, and 44% are in females. \textsuperscript{12}

The company has estimated a UK patient population size of 2,556 and an estimated eligible patient population of 779.\textsuperscript{b}

In the UK in 2016, there were 2,601 deaths from AML.\textsuperscript{14} Five-year relative survival for AML in men in England (14%) is similar to the average for Europe (15%). Five-year relative survival for AML in women in England (16%) is below the average for Europe (18%).\textsuperscript{15}

In England in 2017-2018, there were 47,446 finished consultant episodes (FCE) for acute myeloblastic leukaemia (ICD 10: C92.0), 44,245 hospital admissions and 118,428 FCE bed days.\textsuperscript{16}

AML relapse affects about 50% of all patients who achieved remission after initial treatment, and can occur several months to several years after treatment. However, every patient carries the risk of relapse, and the majority of relapses occur within two to three years of initial treatment.\textsuperscript{17}

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\textsuperscript{b} Information provided by Roche Products Ltd on UK PharmaScan
PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Chemotherapy is the main treatment for AML although bone marrow or stem cell transplant may also be offered.\textsuperscript{18} NICE recommend azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have AML with 20–30\% blasts and multilineage dysplasia. Azacitidine is not recommended, within its marketing authorisation, for treating AML with more than 30\% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.\textsuperscript{19}

CURRENT TREATMENT OPTIONS

Chemotherapy for AML has two phases - induction and consolidation:\textsuperscript{10}
- \textbf{Induction:} the aim of induction is to achieve complete remission (CR). The standard induction chemotherapy regimen is the combination of an anthracycline, usually daunorubicin, given for 3 days with continuous infusion of cytarabine for 7 days (3+7).
- \textbf{Consolidation:} consolidation is designed to eliminate residual leukaemia cells that persist after induction. The standard consolidation regimen is intermediate or high dose cytarabine. Patients might also be given etoposide, daunorubicin, fludarabine, or idarubicin.\textsuperscript{18} After achievement of CR, all patients will eventually relapse without further treatment, and therefore consolidation treatment is essential provided that patients have adequate organ function.\textsuperscript{10}

However, recent European LeukemiaNet (ELN) recommendations state that treatment of patients with relapse AML requires a balance assessment of the likely benefit of further therapy versus the potential complications associated with salvage chemotherapy but no specific salvage regimen has emerged as the standard.\textsuperscript{20}

PLACE OF TECHNOLOGY

If licensed, idasanutlin in addition to cytarabine will offer an additional treatment option for patients with AML whose condition has become refractory to treatments or has relapsed after prior treatments.

CLINICAL TRIAL INFORMATION

<table>
<thead>
<tr>
<th>Trial</th>
<th>MIRROS, NCT02545283, WO29519; idasanutlin in addition to cytarabine versus cytarabine in addition to placebo; phase III</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Source of Information</td>
<td>Trial registry\textsuperscript{3}</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled, double-blind</td>
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<tr>
<td>Participants</td>
<td>N=440 (planned); aged 18 years and older; documented/confirmed first/second refractory/relapsed AML using World Health Organization classification, except acute promyelocytic leukaemia; no more than 2 prior induction regimens (excluding prior hematopoietic stem cell transplant) in their first line treatment and one must have included cytarabine with an anthracycline (or</td>
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anthracenedione); Eastern Cooperative Oncology Group performance status of 0 to 1; adequate hepatic and renal function; white blood cell (WBC) count at randomization less than or equal to (<\=) 50000 cells per cubic millimetre (/mm\(^3\)).

### Schedule

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<th>Randomised to:</th>
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<tr>
<td>• Oral idasanutlin, 300 mg twice daily (in Cycle 1) or once daily (in Cycles 2 and 3) in addition to cytarabine, 1 gram per square meter (g/m(^2)) intravenous (IV) infusion for 5 days of every treatment cycle for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length = 28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length = 28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRI), up to 28 additional days are allowed for blood count recovery, if needed.</td>
</tr>
<tr>
<td>• Placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length = 28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length = 28 days). After each cycle, for participants achieving CRp or CRI, up to 28 additional days are allowed for blood count recovery, if needed.</td>
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### Follow-up

- 3 cycles (treatment cycle length = 28 days); 5 days of treatment followed by 23 days of rest.
- Cycle 1: induction therapy; cycle 2 and 3: consolidation therapy for responding participants.

### Primary Outcomes

- Overall Survival in TP53 wild type (WT) population [Time Frame: Baseline up to approximately 3.5 years]

### Secondary Outcomes

- Overall Survival in the overall population [Time Frame: Baseline up to approximately 3.5 years]
- Percentage of participants in complete remission (CR) at the end of induction according to Hematologic Malignancy Response Assessment (HMRA) in TP53 WT Population [Time Frame: At the end of induction (up to Day 56)]
- Percentage of participants in incomplete platelet count recovery (CRp) at the end of induction according to HMRA in TP53 WT population [Time Frame: At the end of induction (up to Day 56)]
- Percentage of participants with Overall Remission at the end of induction according to HMRA in TP53 WT population [Time Frame: At the end of induction (up to Day 56)]
- EFS according to HMRA in TP53 WT population [Time Frame: Baseline up to treatment failure, relapse or death from any cause (up to approximately 3.5 years)]
- LFS according to HMRA in TP53 WT population [Time Frame: Date of remission to date of relapse or death (up to approximately 3.5 years)]
- Percentage of participants undergoing HSCT following response, in TP53 WT population [Time Frame: Baseline up to approximately 3.5 years]
<table>
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<tr>
<th>Metric</th>
<th>Time Frame</th>
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<tr>
<td>Percentage of participants in CR at the end of induction according to HMRA in overall population</td>
<td>[Time Frame: At the end of induction (up to Day 56)]</td>
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<tr>
<td>Percentage of participants in CRp at the end of induction according to HMRA in overall population</td>
<td>[Time Frame: At the end of induction (up to Day 56)]</td>
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<tr>
<td>Percentage of participants with Overall Remission at the End of Infusion According to HMRA in Overall Population</td>
<td>[Time Frame: At the end of induction (up to Day 56)]</td>
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<tr>
<td>EFS According to HMRA in Overall Population</td>
<td>[Time Frame: Baseline up to treatment failure, relapse or death from any cause (up to approximately 3.5 years)]</td>
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<tr>
<td>LFS According to HMRA in Overall Population</td>
<td>[Time Frame: Date of remission to date of relapse or death (up to approximately 3.5 years)]</td>
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<tr>
<td>Percentage of Participants Undergoing HSCT Following Response, in Overall Population</td>
<td>[Time Frame: Baseline up to approximately 3.5 years]</td>
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<td>Apparent Clearance (CL/F) of Idasanutlin</td>
<td>[Time Frame: Cycle 1: Predose (0 hour [Hr]), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]</td>
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<tr>
<td>Apparent Volume of Distribution (Vd/F) of Idasanutlin</td>
<td>[Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]</td>
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<tr>
<td>Maximum Concentration Observed (Cmax) of Idasanutlin</td>
<td>[Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]</td>
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<tr>
<td>Steady-State Concentration (C trough) of Idasanutlin</td>
<td>[Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]</td>
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<tr>
<td>Area Under the Concentration-Time Curve (AUC) During One Dosing Interval (AUCtau) of Idasanutlin</td>
<td>[Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]</td>
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</table>
- AUC from Time Zero to 24 Hours Post Dose (AUC0-24) of Idasanutlin
  [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]

- Half-Life (t 1/2) of Idasanutlin
  [Time Frame: Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)]

- Total Clearance (CL) of Cytarabine
  [Time Frame: Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)]

- Volume of Distribution (Vd) of Cytarabine
  [Time Frame: Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)]

- Percentage of Participants with Adverse Events
  [Time Frame: Baseline up to approximately 3.5 years]

- Change from Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Score
  [Time Frame: Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)]

- Change from Baseline in EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire Score
  [Time Frame: Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)]

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<tr>
<th>Key Results</th>
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<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
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<tr>
<td>Expected reporting date</td>
<td>Estimated primary completion date reported as December 2019. Study completion date reported as May 2021.</td>
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</table>

**ESTIMATED COST**

The cost of idasanutlin is not yet known.
NICE GUIDANCE

- NICE technology appraisal in development. Ivosidenib for treating relapsed or refractory IDH1-positive acute myeloid leukaemia (ID1548). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Quizartinib for treating relapsed or refractory acute myeloid leukaemia (ID1325). Expected date of issue to be confirmed.
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE


OTHER GUIDANCE

REFERENCES


NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.