Laromustine (Onrigin) for acute myeloid leukaemia in newly diagnosed elderly patients - induction therapy

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Laromustine (Onrigin) for acute myeloid leukaemia in newly diagnosed elderly patients - induction therapy

Target group
- Acute myeloid leukaemia (AML) in elderly patients (aged ≥60); newly diagnosed with poor-risk features (no secondary AML and one or more of: unfavourable cytogenetics, ECOG performance status [PS] of 2 and significant co-morbidities) - induction therapy.

Technology description
Laromustine (Onrigin, Cloretazine, VNP-4010M) is a small molecule sulfonyle hydrazine prodrug (SHP) and is first in a new class of agents within the alkylating group. In two phase II clinical trials, laromustine is administered intravenously (IV) at 600mg/m² over 30-60 minutes on day 1 (course 1) as induction therapy.

Laromustine is in phase III clinical trials in combination with cytarabine (ara-c) in patients with relapsed AML, and as a monotherapy for standard remission induction therapy in patients aged 18 to 65 with previously untreated AML and high-risk myelodysplasia (MDS). Laromustine is also in phase II clinical trials for glioma.

Innovation and/or advantages
If licensed, laromustine will be one of the first treatments specifically for this indication, and may provide durable remissions with less toxicity and better outcomes than standard therapy.

Developer
Vion Pharmaceuticals, Inc.

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

NHS or Government priority area:
The topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007), and the National Service Framework for Older People (2001).

Relevant guidance
- NICE cancer service guideline. Haemato-oncology. 2003¹.
- Department of Health: Specialised Services National Definition Set: 2. Specialised services for blood and marrow transplantation (all ages). 2007².

Clinical need and burden of disease
AML is a form of bone marrow cancer where the malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood forms and replacement of normal marrow by malignant cells.

The UK incidence of adults with AML is 10 per 100,000 of the population per year⁴ (around 1,950 cases per year). Approximately half are over 68 years, and around 70% of
elderly patients are not offered intensive chemotherapy because they are generally not considered to be fit enough.\(^a\)

The therapeutic results for patients over 60 years accrued into clinical trials of intensive chemotherapy are largely unsatisfactory with complete remission rates rarely over 50–60%; median relapse-free survival usually less than 12 months.\(^5\) The median survival of patients who are not treated with intensive chemotherapy, who do not achieve remission or who relapse, is two to three months.\(^a\)

### Existing comparators and treatments

Best supportive care (BSC) includes:

- **Hydroxyurea** - provides 0% complete response (CR) and a median survival of 2-3 months.
- **Low dose ara-c (LDAC)** - achieves complete remission in around 18% with a median survival of 20 months.

Other treatments (though rarely offered for high-risk elderly patients) include:

- Stem cell transplantation
- Intensive chemotherapy

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>VION-CLI-043; NCT00354276(^6,7,8); laromustine induction therapy; phase II.</th>
<th>VION-CLI-033; NCT00083187(^7,9); laromustine induction therapy; AML or MDS; phase II.</th>
<th>NCT00655395(^8); laromustine and ara-C induction therapy; phase I/II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Vion Pharmaceuticals.</td>
<td>Vion Pharmaceuticals.</td>
<td>Vion Pharmaceuticals.</td>
</tr>
<tr>
<td>Location</td>
<td>North America and Europe.</td>
<td>USA.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Open-label; uncontrolled.</td>
<td>Open-label; uncontrolled.</td>
<td>Open-label; uncontrolled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=85; elderly (aged ≥70); previously untreated; newly diagnosed poor risk AML. Laromustine 600mg/m(^2) IV induction therapy as 60 minute infusion on day 1 (course 1). Second induction cycle, between days 35-60, for those with partial response (PR) or haematologic improvement (HI). Patients with complete response (CR) or partial CR (CRp) received consolidation therapy, beginning between days 45-90, with ara-C 400mg/m(^2) daily IV for 5 days.</td>
<td>n=131; elderly (aged ≥60); previously untreated; AML or high-risk MDS. Laromustine 600mg/m(^2) IV induction therapy over 30 minutes on day 1 (course 1). Second induction cycle at 4-5 weeks if improved. If CRp achieved, laromustine 400mg/m(^2) consolidation course considered.</td>
<td>n=52; elderly (aged ≥60) previously untreated AML &gt;20% blasts in bone marrow or blood. Laromustine 300, 400 or 500mg/m(^2) IV on day 1, and ara-C 100mg/m(^2) for 7 days.</td>
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<tr>
<td>Follow-up</td>
<td>12 months.</td>
<td>6 months, 1 year, and 18 months.</td>
<td>2 years.</td>
</tr>
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</table>

\(^a\) Expert opinion.

\(^b\) Information from the company.
<table>
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<tr>
<th>Primary outcomes</th>
<th>Overall response rate (ORR). ORR; safety. ORR.</th>
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<tr>
<td>Secondary outcomes</td>
<td>Leukaemia free survival (LFS); overall survival (OS). LFS; OS. Safety.</td>
</tr>
<tr>
<td>Key results</td>
<td>ORR: 31.8%. LFS: 62.5% at 3 months, 53.2% at 6 months, 38.7% at 9 months and 27.6% at 12 months. OS: 54.1% at 3 months, 35.3% at 6 months, 28.2% at 9 months, and 21.1% at 12 months. Induction mortality within 30 days: 14.1%. ORR: 38.2%. LFS: 70.0% at 3 months, 40.0% at 6 months, 40.0% at 9 months and 28.6% at 12 months. OS: 55.8% at 3 months, 33.5% at 6 months, 24.2% at 9 months, and 22.1% at 12 months. Induction mortality within 30 days: 14.5%.</td>
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<tr>
<td>Expected reporting date</td>
<td>Pending publication in 2009. -</td>
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<td>Adverse effects</td>
<td>Most common AEs: gastrointestinal disturbances, myelosuppression, and respiratory events. Serious AEs: febrile neutropenia (21.3%), pneumonia (8.7%), thrombocytopenia (5.4%), dyspnoea (6.5%) and pyrexia (9.0%).</td>
</tr>
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</table>

**Estimated cost and cost impact**
The cost of laromustine is not yet known.

**Potential or intended impact – speculative**

**Patients**
- ✔ Reduced morbidity
- ✔ Reduced mortality or increased survival
- ✔ Improved quality of life for patients and/or carers
- □ Quicker, earlier or more accurate diagnosis or identification of disease
- □ Other:
- □ None identified

**Services**
- □ Increased use:
- □ Service reorganisation required
- □ Staff or training required
- □ Decreased use
- □ Other:
- □ None identified

**Costs**
- ✔ Increased unit cost compared to alternative (BSC)
- ✔ Increased costs: more patients coming for treatment (vs BSC)
- □ Increased costs: capital investment needed
- □ New costs:
- □ Savings:
- □ Other:
- □ None identified

**References**

