Ruxolitinib (Jakavi) for polycythaemia vera – second line

SUMMARY

Ruxolitinib (Jakavi) is intended to be used as second line therapy for the treatment of polycythemia vera (PV) resistant to, or intolerant of, hydroxyurea. If licensed, it may offer an additional treatment option for this patient group. It is an inhibitor of Janus kinase (JAK) 1 and 2. JAKs are protein tyrosine kinases which are involved in specific cytokine-receptor signalling pathways and are often up-regulated in myeloproliferative disorders. Ruxolitinib is licensed in the UK for the treatment of disease-related splenomegaly or other symptoms in adult patients with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

PV is a myeloproliferative disorder (MPD), which are chronic clonal haematological malignancies characterised by overproduction of mature blood cells. Worldwide estimates of the incidence of MPDs vary greatly, with the incidence of PV approximately at 2.0-2.8 per 100,000 in the UK. The incidence is slightly higher in males than females and the median age at presentation is 55-60 years. In 2011-12, there were 15,372 admissions for PV in England, resulting in 876 bed-days and 15,459 finished consultant episodes. The median survival in untreated symptomatic patients after diagnosis is six to 18 months, with treatment the median survival is more than 10 years. The population likely to be eligible to receive ruxolitinib could not be estimated from available sources.

Current guidelines state that the main aims of treatment for PV is to minimise the risk of transformation to acute leukaemia and myelofibrosis, and to reduce the risk and manage complications of thrombosis, haemorrhage and pruritus. Pharmacological treatments include hydroxyurea (hydroxycarbamide) and interferon alpha. Ruxolitinib is currently in two phase III clinical trials comparing its effect on symptoms and spleen volume against treatment with hydroxyurea and best available therapy. These trials are expected to complete in Q3 2013.
TARGET GROUP

- Polycythaemia vera - second line; in patients who are resistant to, or intolerant of, hydroxyurea.

TECHNOLOGY

DESCRIPTION

Ruxolitinib (Jakavi; INC424; INCB18424) is an inhibitor of Janus kinase (JAK) 1 and 2. JAKs are protein tyrosine kinases which are involved in specific cytokine-receptor signalling pathways and are often up-regulated in myeloproliferative disorders. It is intended for the second line treatment of polycythaemia vera (PV) in patients who are resistant to, or intolerant of, hydroxyurea. Ruxolitinib is administered orally at 10-25mg twice a day.

Ruxolitinib is licenced in the UK for the treatment of disease-related splenomegaly or other symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post PV myelofibrosis or post essential thrombocythaemia myelofibrosis. Ruxolitinib is in phase II clinical trials for the treatment of pancreatic cancer, advanced acute lymphocytic leukaemia, advanced, relapsed and/or refractory acute myeloid leukaemia, psoriasis and essential thrombocythaemia.

The most frequent treatment-related adverse events (AEs) associated with ruxolitinib when used for its licensed indication include: anaemia; thrombocytopenia; neutropenia; bruising; dizziness; headache; urinary tract infections; flatulence; and hypercholesterolaemia.

INNOVATION and/or ADVANTAGES

Ruxolitinib is a new class of oral treatment for patients with PV, and if licensed it may offer an additional treatment option for this patient group.

DEVELOPER

Novartis (EU/UK licence holder); Incyte Corporation.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

The myeloproliferative disorders (MPDs) are chronic clonal haematological malignancies characterised by overproduction of mature blood cells. They include PV, primary myelofibrosis (PMF) and essential thrombocythaemia (ET). These disorders are closely linked; many patients share a common mutation of the JAK 2 gene in the early haemopoietic stem cell (approximately 95% of PV patients). In addition to their shared features, PV, ET, and PMF can mimic each other clinically, and their clinical phenotypes are also subject to
change with time. Both PV and ET may transform to myelofibrosis (MF) and there is also a risk of transformation to acute myeloid leukaemia (AML)\(^3,^a\).

In PV, hypercatabolism and hyperviscosity resulting from excessive red cell production and concomitant thrombocytosis and leucocytosis, lead to headache, fatigue, dizziness, pruritus, excessive sweating, and erythromelalgia\(^3,^4\).

### NHS or GOVERNMENT PRIORITY AREA

None identified.

### CLINICAL NEED and BURDEN OF DISEASE

Worldwide estimates of the incidence of MPDs vary greatly, with the incidence of PV approximated at 2.0-2.8 per 100,000 in the UK\(^5,^a\). The incidence is slightly higher in males than females\(^a\) and the median age at presentation is 55-60 years\(^2\). Over 10-15 years, MF occurs in 10-15% of cases and the disease transforms to AML in 5-10%\(^2\).

In 2011-12, there were 15,372 admissions for PV (ICD-10 D45) in England, resulting in 876 bed-days and 15,459 finished consultant episodes\(^6\). Expert opinion suggests that most hospital haematology departments in the UK manage around 70 patients with PV\(^a\). The median survival in untreated symptomatic patients after diagnosis is 6 to 18 months; with treatment the median survival is more than 10 years\(^7\). The population likely to be eligible to receive ruxolitinib could not be estimated from available sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance

- NICE technology appraisal in development. Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (ID510). Expected June 2013\(^8\).

#### Other Guidance

- European LeukaemiaNet consensus statement for the diagnosis and management of MPD. 2011\(^9\).
- British Committee for Standards in Haematology. Guidelines for the diagnosis, investigations and management of polycythaemia/erythrocytosis. 2005\(^10\).

### EXISTING COMPARATORS and TREATMENTS

Current guidelines state that the main aims of treatment for PV is to\(^10\):

- Minimise the risk of transformation to acute leukaemia and myelofibrosis.
- Reduce the risk and manage the complications of thrombosis, haemorrhage and pruritus.

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\(^a\) Expert personal communication.
Options include\textsuperscript{10,11}:
\begin{itemize}
\item Repeated phlebotomy.
\item Reduction of blood clot risk – low-dose acetylsalicylic acid, warfarin.
\item Chemotherapy – hydroxyurea, busulphan, melphalan. Expert opinion states that alkylating agents are not recommended in patients below 70 as they can induce leukaemia after 5-10 years\textsuperscript{b}.
\item Radiotherapy and radioactive phosphorus 32P – most often used in the elderly.
\item Interferon alpha – supresses the proliferation of both pluripotent and lineage-committed haematopoietic progenitors. First line therapy for PV patients <40 years old and used during pregnancy\textsuperscript{12,6}.
\end{itemize}

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>RELIEF, NCT01632904, 18424-357, EUCTR2012-002318-37-GB; ruxolitinib vs hydroxyurea; phase III.</th>
<th>RESPONSE, NCT01243944, CINC424B2301, EUCTR2010-020807-57-BE; ruxolitinib vs best available therapy; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Incyte Corporation.</td>
<td>Incyte Corporation.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{13}.</td>
<td>Trial registry\textsuperscript{14}.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>EU (incl UK), USA, and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=110 (planned); 18 years and older; PV; PV symptoms while on a stable dose of hydroxyurea (HU).</td>
<td>n=200 (planned); 18 years and older; PV; resistant to, or intolerant of hydroxyurea.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to ruxolitinib 10mg in combination with HU-placebo, or HU\textsuperscript{c} in combination with ruxolitinib-placebo, all oral, twice daily.</td>
<td>Randomised to ruxolitinib at a starting dose of 10mg oral twice daily, with individualised dose titration to a final dose ranging from 5mg oral once daily, to 25mg oral twice daily\textsuperscript{d}; or best available therapy\textsuperscript{e}.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 16 weeks, with option of 32 week extension.</td>
<td>Active treatment period 80 weeks.</td>
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<tr>
<td>Primary outcome/s</td>
<td>$\geq$ 50% reduction in a cluster of PV-related symptoms.</td>
<td>Reduction in spleen volume and absence of phlebotomy eligibility.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Improvement in individual PV-related symptoms; duration of improvement in PV-related symptoms; duration of symptomatic improvement from individual symptoms; changes in cytokines; safety.</td>
<td>Complete haematological remission; durable spleen volume reduction; durable phlebotomy independence; overall clinico-haematologic response rate; durable complete or partial clinico-haematologic response; safety.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as Sept 2013.</td>
<td>Primary completion data reported as Aug 2013.</td>
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</tbody>
</table>

\textsuperscript{b} Expert personal communication.

\textsuperscript{c} Participants continue on the same HU dose as prior to start of study.

\textsuperscript{d} Dose is based on safety and efficacy.

\textsuperscript{e} Best available therapy will be selected by the investigator for each subject and may include: hydroxyurea; Interferons/peg-interferon (IFN/PEG-IGN); pipobroman; anagrelide; immunomodulatory drugs (IMIDs); observation.
### Source of information
Abstract, trial registry.

### Location
USA and Italy.

### Design
Randomised.

### Participants
n=73; 18 years and older; PV (or ET); resistant to, or intolerant of, hydroxyurea.

### Schedule
Randomised to ruxolitinib 10mg, 25mg or 50mg oral twice daily for 56 days, then investigators adjust dose/regimen on an individual basis.

### Follow-up
Active treatment period until progression.

### Primary outcome/s
Partial and complete response (CR).

### Secondary outcome/s
Individual components of clinical response at week 12, 24 and 36; change in PV symptoms as rated on a scale of 0 (none) to 10 (worse possible); quality of life (QoL)\(^g\).

### Key results
For ruxolitinib 10mg, 25mg and 50mg respectively: partial and CR, 58%, 50%, 57%; individual components of CR at week 12: haematocrit (Hct) <45% without phlebotomy, 95%, 88%, 86%; absence of palpable splenomegaly, 68%, 50%, 57%; 50% reduction in spleen size, 74%, 63%, 86%; platelet count ≤400 x 10\(^9\)/L, 58%, 50%, 57%; white blood cell (WBC) count ≤10 x 10\(^9\)/L, 68%, 63%, 43%; individual components of CR at week 24: Hct <45% without phlebotomy, 100%, 88%, 100%; absence of palpable splenomegaly, 61%, 43%, 71%; 50% reduction in spleen size, 78%, 71%, 100%; platelet count ≤400 x 10\(^9\)/L, 58%, 88%, 86%; WBC count ≤10 x 10\(^9\)/L, 74%, 25%, 86%; individual components of CR at week 36: Hct <45% without phlebotomy, 100%, 88%, 100%; absence of palpable splenomegaly, 71%, 57%, 86%; 50% reduction in spleen size, 75%, 71%, 100%; platelet count ≤400 x 10\(^9\)/L, 67%, 75%, 86%; WBC count ≤10 x 10\(^9\)/L, 67%, 25%, 71%; change in PV symptoms (mean ± SD): pruritus, -4.2 ± 3.63, -4.6 ± 1.85, -2.8 ± 4.09; bone pain, -2.0 ± 1.95, -2.5 ± 0.71, -4.3 ± 2.08; fever, -2.0 ± 1.41, NA ± NA\(^h\), -20. ± 1.41; night sweats, -1.9 ± 2.52, -2.8 ± 3.19, -3.3 ± 1.15; QoL score (mean ± SD), 10.9 ± 10.80, 6.3 ± 14.0, 14.6 ± 17.78.

### Adverse effects (AEs)
AEs include: anaemia, thrombocytopenia, neutropenia, leukopenia, diarrhoea, vomiting, abdominal pain, pyrexia, dizziness, headache.

### ESTIMATED COST and IMPACT

#### COST
Ruxolitinib is licensed in the UK for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (MF), post PV MF or post essential thrombocythaemia MF; a pack of 60 x 5mg tablets cost £1,800 and a pack of 60 x 15mg or 20mg tablets cost £3,600. Treatment with 10mg twice daily for 30 days would cost £3,600, and treatment with 25mg twice daily for 30 days would cost £5,400\(^17\).

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
- No impact identified

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\(^f\) Individual components of clinical response include: haematocrit (Hct) <45% without phlebotomy; absence of palpable splenomegaly; 50% reduction in spleen size; platelet count ≤400 x 10\(^9\)/L; white blood cell (WBC) count ≤10 x 10\(^9\)/L.

\(^g\) Health related quality of life was assessed using the global health status/quality of life scale of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

\(^h\) No patients in this group had a baseline score > 0.
Impact on Services

- Increased use of existing services: Decreased use of existing services: expert opinion indicates that if ruxolitinib replaces need for phlebotomy, then it will reduce the demand on NHS service delivery.
- Re-organisation of existing services: Need for new services
- Other: None identified

Impact on Costs

- Increased drug treatment costs: Reduced drug treatment costs
- Other increase in costs: Other reduction in costs: expert opinion suggests that there may be reduction in treatment costs if ruxolitinib reduces risk of PV transforming into MF or AML.
- Other: None identified

Other Issues

- Clinical uncertainty or other research question identified: None identified

REFERENCES


