Health Technology Briefing
February 2022

Navitoclax with ruxolitinib for myelofibrosis

Company/Developer	AbbVie Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28726	NICE ID: 10567	UKPS ID: 660451

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Navitoclax in combination with ruxolitinib is currently in clinical development for the treatment of intermediate-2 or high-risk primary myelofibrosis (PMF), post polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Myelofibrosis is a rare blood cancer that causes scarring of the bone marrow, which makes it more difficult to produce blood cells. The clinical features of myelofibrosis are variable. Allogeneic hematopoietic cell transplant is currently the only curative method. The current standard of care for those unsuitable for stem cell transplant is treatment with ruxolitnib. However, many patients do not achieve an adequate response to this drug, and significant residual symptoms remain. There is, therefore, an urgent need for an improvement in therapeutic approaches for myelofibrosis.

Navitoclax blocks the activity of a group of proteins called Bcl-2, which normally prevent cells from dying. When used together with chemotherapy or radiation, the medicine is expected to promote cell death and increase the ability of these treatments to kill cells, thereby increasing their effectiveness in treating the disease. Both navitoclax and ruxolitnib will be administered orally. If approved, this will provide an alternative treatment option for myelofibrosis patients ineligible for stem cell transplant.

Proposed Indication

Treatment of intermediate-2 or high-risk primary myelofibrosis (PMF), post polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis for patients who are ineligible for stem cell transplant.[1-3]

Technology

Description

Navitoclax (ABT-263) is an orally active dual inhibitor of the antiapoptotic proteins, BCL-XL and BCL-2.[4] Navitoclax binds to the BH3 binding groove of BCL-2 proteins which are located in the cytoplasm, causing the displacement of pro-apoptotic BH3-only protein, BIM, from BCL-2. BIM is then set free to trigger the release of small heme proteins, the cytochrome c, from mitochondria causing cell apoptosis.[5]

Navitoclax in combination with ruxolitinib is currently in clinical development for the treatment of intermediate-2 or high-risk primary myelofibrosis, post polycythaemia vera or post-essential thrombocythemia myelofibrosis. In the phase II trial (NCT03222609), navitoclax is administered orally once daily at various doses and a dose greater than or equal to 10 mg of ruxolitinib orally twice daily.[1]

Key Innovation

Navitoclax is a novel anti-apoptotic B cell leukaemia 2 (Bcl-2) inhibitor that, when combined with ruxolitinib in phase II trials, has shown significant promise in the treatment of intermediate-2 to high-risk myelofibrosis.[6,7]

Allogeneic haematopoietic cell transplant is the only curative method for those at higher risk with PMF. However, the procedure is associated with a higher risk of procedure-related complications, limiting those who may be eligible for this therapy. In lower-risk PMF or higher-risk patients who are ineligible for allogeneic haematopoietic cell transplant, treatment is generally symptom-guided.[6] The current NHS standard of care for those unsuitable for stem cell transplant is treatment with ruxolitnib. However, many patients do not achieve an adequate response to this drug, and significant residual symptoms remain. There is, therefore, an urgent need for an improvement in therapeutic approaches for myelofibrosis patients.[8]

Regulatory & Development Status

Navitoclax is not currently have Marketing Authorisation in the EU/UK for any indication.

Navitoclax has received an orphan drug designation in the EU in 2019 for myelofibrosis.[9]

Patient Group

Disease Area and Clinical Need

Myelofibrosis is a rare blood cancer. It causes scarring of the bone marrow which makes it more difficult to produce blood cells. It is one of a group of conditions called myeloproliferative neoplasms or myeloproliferative disorders.[10] It primarily affects middle-aged and elderly people and is hardly ever diagnosed in children.[11] Primary myelofibrosis is when individuals who have no history of problems with their bone marrow get myelofibrosis. Secondary myelofibrosis is where the condition develops in people who have other bone marrow disorders such as polycythaemia vera or essential thrombocythaemia. Some research suggests that exposure to the chemical benzene may the risk of developing myeloproliferative neoplasms. More than 55% of people with myelofibrosis have a change in a gene called JAK2. The JAK2

gene makes a protein that controls how many blood cells the stem cells make. Up to 35% have a change in the CALR gene. When the JAK2 or CALR gene becomes mutated, the bone marrow may not function correctly.[12] The clinical features of myelofibrosis are variable and include progressive anaemia, leucopaenia or leucocytosis, thrombocytopaenia or thrombocytosis and multi-organ extramedullary haemopoiesis, most commonly causing hepatomegaly and symptomatic splenomegaly. Patients with advanced disease experience severe constitutional symptoms, the consequences of massive splenomegaly (pain, early satiety, splenic infarction, portal hypertension and dyspnoea), progressive marrow failure, pulmonary hypertension, transformation to leukaemia and early death.[13]

The number of people diagnosed each year with myelofibrosis will be two to three cases per 100,000 and it is equally common in men and women.[11] The median age at diagnosis is 60 years and more than 90% of patients are diagnosed after age 40 years, however myelofibrosis has been reported in all age groups.[11,14]

Recommended Treatment Options

Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment. Other treatment options aim to relieve symptoms and improve quality of life. These include hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion.[15]

NICE recommends ruxolitinib as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis, only in people with intermediate-2 or high risk disease.[15,16] NICE also recommends fedratinib for use within the Cancer Drugs Fund as an option for treating disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis in adults. It is recommended only if they have previously had ruxolitinib and the conditions in the managed access agreement for fedratinib are followed.[17]

Clinical Trial Information

Trial	**TRANSFROM-1,** NCT04472598, **EudraCT-**2020-000097-15**;** A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Of Navitoclax In Combination With Ruxolitinib Versus Ruxolitinib In Subjects With Myelofibrosis (TRANSFORM-1) **Phase III –** Recruiting **Location(s) –** 11 countries in EU, UK, US, Canada and other countries **Primary completion date –** July 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 230; documented diagnosis of PMF as defined by World Health Organization (WHO) classification or Secondary myelofibrosis (post polycythemia vera [PPV] - myelofibrosisor Post Essential Thrombocytopenia [PET] - myelofibrosis); 18 years and older
Intervention(s)	Oral navitoclax in combination with oral ruxolitinib
Comparator(s)	Placebo for navitoclax in combination with ruxolitinib
Outcome(s)	Percentage of participants who achieve spleen volume reduction of at least 35% at week 24 (SVR35W24) [Time frame: at week 24]

	See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**TRANSFORM-2, NCT04468984, EudraCT-2020-000557-27;** A Randomized, Open-Label, Phase 3 Study Evaluating Efficacy and Safety of Navitoclax in Combination With Ruxolitinib Versus Best Available Therapy in Subjects With Relapsed/Refractory Myelofibrosis (TRANSFORM-2) **Phase III –** Recruiting **Location(s) –** 14 countries in EU, UK, US, Canada and other countries **Primary completion date –** April 2023
Trial Design	Randomised, parallel assignment, open label
Population	N = 330; documented diagnosis of primary myelofibrosis as defined by the WHO classification, PPV-MF, or PET-MF; classified as intermediate-2 or high-risk myelofibrosis, as defined by the Dynamic International Prognostic Scoring System Plus (DIPSS+); 18 years and older
Intervention(s)	Oral navitoclax tablets once daily with oral ruxolitinib tablets twice daily.
Comparator(s)	Best available therapy
Outcome(s)	Percentage of participants who achieve spleen volume reduction of at least 35% at week 24 (SVR35W24) [Time frame: at week 24] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**REFINE, NCT03222609, EudraCT-2017-001398-17;** A Phase 2 Open-Label Study Evaluating Tolerability and Efficacy of Navitoclax Alone or in Combination With Ruxolitinib in Subjects With Myelofibrosis (REFINE) **Phase II** – Active, not recruiting **Locations(s) –** 9 countries in EU, UK US, Canada and other countries **Primary completion date –** April 2022
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 191; participants with documented diagnosis of intermediate-2 or high-risk primary myelofibrosis, post polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, 18 years and older
Intervention(s)	Oral navitoclax once daily at various doses and a dose greater than or equal to 10 mg of oral ruxolitinib twice daily
Comparator(s)	Oral navitoclax once daily

Outcome(s)	Percentage of participants who achieve spleen volume reduction of greater than or equal to 35% (SVR35) from baseline [Time frame: from baseline (week 0) through week 24] See trial record for full list of all outcomes
Results (efficacy)	Spleen volume reduction of ≥35% (SVR_{35}) from baseline (BL) to week (wk) 24 was reported for 9 (27%) patients, independent of high molecular risk mutations (HMR), and SVR_{35} at any time was achieved in 15 (44%) patients; responses were seen at wk 12 in 6 (18%) patients.. Median duration of response (DOR) of SVR_{35} was 13.8 months (95% confidence interval [CI]: 8.2–not reached), which was similar in patients with and without HMR. Total symptom score (TSS) was reduced by ≥50% in 6/20 (30%) patients who were evaluable at wk 24. Bone marrow fibrosis (BMF) improved by ≥1 grade at any time on study in 11/33 (33%) patients. Haemoglobin (Hgb) levels improved on-study; 7/11 (64%) patients with Hgb <10 g/dL or transfusion dependency at BL had improvement in Hgb of ≥2 g/dL (n=6) or became transfusion independent (TI) (n=1). At a median follow-up of 105 wks, median OS was not reached; overall survival (OS) estimate at 24 months was 84% (95% CI: 63.0%–93.9%).[18]
Results (safety)	All patients experienced an adverse event (AE), most common AEs were thrombocytopenia (88%), diarrhoea (71%), and fatigue (62%), with most gastrointestinal AEs of Grade 1/2. Thirty (88%) patients experienced a Grade 3/4 AE, and 15 (44%) had a serious AE (SAE). The most common Grade ≥3 AEs were thrombocytopenia (without clinically significant bleeding; 56%) and anaemia (32%), and the most common SAE was pneumonia (12%). Thrombocytopenia led to navitoclax dose reduction in 19 (56%) patients.[18]

Estimated Cost

The price of navitoclax is not yet known.

The NHS indicative price of 56 10mg, 15mg or 20mg ruxolitinib tablets is £2856.00.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (TA756). December 2021.
- NICE technology appraisal. Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (TA386). March 2016.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Pan-London Blood Cancer. Pan-London Haemato-Oncology Clinical Guidelines. January 2020.[20]

- British Society for Haematology. Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012. June 2014.[21]
- British Society for Haematology. Guideline for the diagnosis and management of myelofibrosis. June 2012.[13]

Additional Information

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