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# HEALTH TECHNOLOGY BRIEFING
# AUGUST 2021

# Sabatolimab in addition to azacitidine for myelodysplastic syndromes – first-line

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| **NIHRIO ID** | 29698 | **NICE ID** | 10671 |
| **Developer/Company** | Novartis Pharmaceuticals UK Ltd | **UKPS ID** | 660899 |

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| **Licensing and market availability plans** | Currently in phase III/II clinical trials. |

## SUMMARY


Sabatolimab in addition to azacitidine is in clinical development for the treatment of higher risk myelodysplastic syndromes (MDS) in adults. Myelodysplastic syndromes are a group of cancers in which immature blood cells in the bone marrow do not mature or become healthy blood cells. MDS are long-term debilitating and life-threatening diseases

Sabatolimab targets an inhibitory receptor that regulates adaptive and innate immune responses. Azacitidine is already approved for MDS and the addition of sabatolimab may provide synergistic efficacy and safety. If licensed, sabatolimab in addition to azacitidine will offer an additional treatment option for patients with untreated higher risk who currently have few well-tolerated effective therapies available.


## PROPOSED INDICATION

Treatment of patients with untreated higher risk myelodysplastic syndromes (MDS).[1]

# TECHNOLOGY

## DESCRIPTION

Sabatolimab (MBG453) is a high-affinity, humanized, IgG4 (S228P) antibody targeting TIM-3, an inhibitory receptor that regulates adaptive and innate immune responses.[2] TIM-3 is an immune checkpoint with a complex regulatory role in both adaptive and innate immune responses and is also preferentially expressed on leukemic stem and progenitor cells, making it a potential target in myelodysplastic syndromes (MDS).[3]

In the phase III trial (NCT04266301; STIMULUS-MDS2), a dose of sabatolimab 800 mg will be administered intravenously (IV) every 4 weeks, and a dose of azacitidine 75 mg/m$^2$ is administered IV or subcutaneously (SC) on day 1-7, or day 1-5, 8 and 9.[1]

## INNOVATION AND/OR ADVANTAGES

Sabatolimab is promising target for higher risk MDS and acute myeloid leukemia (AML) as it is high-affinity humanized anti-TIM-3.[3]

In a phase I study (NCT03066648) Sabatolimab + hypomethylating agents (HMAs) was shown to be well tolerated in patients with AML and higher risk MDS and continues to show promising antileukemic activity and emerging durability.[4]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sabatolimab is not currently licensed for any indications in the EU/UK.

Azacitidine is currently licensed for the treatment of the following indications in the UK:[5]

- adult patients who are not eligible for haematopoetic stem cell transplantation (HSCT) with intermediate-2 and high-risk MDS
- chronic myelomonocytic leukaemia (CMML) with 10- 29% marrow blasts without myeloproliferative disorder
- AML with 20-30% blasts and multi-lineage dysplasia
- AML with >30% marrow blasts

Common adverse events, i.e., occur for more than 10 in 100 people, of azacitidine include: lung infection, inflammation of the nose and throat, breathlessness, risk of infection, bruising and bleeding, loss of appetite and weight loss, difficulty sleeping, dizziness and headaches, diarrhoea or constipation, feeling or being sick, abdominal pain, rash, itchy skin, joint and muscle pain, high temperature, tiredness, chest pain, redness, pain and swelling at the injection site.[6]

Sabatolimab with azacitidine are in phase II clinical development for AML.[7]

# PATIENT GROUP

## DISEASE BACKGROUND

MDS are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections.[8]

Although risk factors often influence the development of MDS, most do not directly cause MDS. Some people with several risk factors never develop MDS, while others with no known risk factors do.[9]

The following factors may raise a person's risk of developing MDS:[9]

- Age. MDS occurs most often in people older than 60 and is less common in younger people. MDS is rare in children
- Gender. Men develop MDS more often than women
- Exposure to environmental/occupational hazards. Long-term exposure to benzene, tobacco smoke, insecticides, and other toxins may increase the risk of developing MDS
- Previous chemotherapy or radiation treatment. Approximately 20% of people who develop MDS previously received chemotherapy or radiation therapy. This type of MDS is called secondary
- Genetics. Most often, MDS is not inherited, meaning passed from parent to child within a family. However, some genetic changes may increase a person's risk of developing MDS. Many of these are linked with the inherited genetic conditions listed below, with the specific genes involved when identified. Research continues to identify other likely genetic factors.
- Fanconi anemia
- Familial MDS/AML (GATA2, DDX41)
- Thrombocytopenia 2 (ANKRD26)
- Thrombocytopenia 5 (ETV6)
- Familial aplastic anemia (SRP72)
- Shwachman-Diamond syndrome
- Diamond Blackfan anemia
- Congenital neutropenia
- Familial platelet disorder

High risk MDS can develop into AML if the number of blast cells in the blood rises above 20%.[10] AML is a rapidly growing cancer of the blood and bone marrow, with a poor prognosis if left untreated. Around 30% of patients with MDS progress to AML.[11]

Most patients with MDS are affected by anaemia and anaemia-related symptoms, which negatively impact health-related quality of life (QoL).[12] The symptoms can include: weakness, tiredness and occasional breathlessness (because of the low number of red blood cells); frequent infections (because of the low number of white blood cells); bruising and easy bleeding, such as nosebleeds (because of the low number of platelets).[13]

## CLINICAL NEED AND BURDEN OF DISEASE

The annual incidence of MDS is estimated at 4 per 100,000, but incidence increases with age and is 30 per 100,000 per year in people over 70 years of age. Many cases remain undiagnosed.[14] In 2017, there were 2,385 registrations of newly diagnosed cases of MDS (ICD-10 code: D46) and the direct age-standardised rate per 100,000 population of newly diagnosed cases was 6.7 among males and 3.0 among females in England.[15]

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 61,336 finished consultant episodes (FCE) for MDS (ICD-10 code: D46), resulting in 59,794 hospital admissions and 24,174 FCE bed days and 52,892 day cases.[16] At the time of EU Orphan designation, MDS affected less than 2 in 10,000 people in the EU. This was equivalent to a total of fewer than 104,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000.[17]

In 2019 there were 1,126 deaths registered with MDS as the final underlying cause in England and Wales.[18]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

Treatment goals for patients with MDS are two-fold: improve peripheral blood values (i.e., increase haemoglobin levels and reduce bleeding and infections) and change the natural progression of the disease. The choice of therapy for newly diagnosed and relapsed/refractory MDS depends on the individual patient's risk classification, fitness (including comorbidities), goals and preferences, caregiver and social support, and suitability for hematopoietic cell transplantation (HCT).[12]

For patients with higher risk MDS, the treatment priority is changing the natural history of the disease by delaying disease progression, improving overall survival, and proceeding to HCT, if possible, to potentially achieve a cure. Before initiating treatment for high risk MDS, patients should be evaluated for candidacy for HCT, including age and comorbidities. All patients, regardless of risk, should receive supportive care measures as part of the MDS therapeutic algorithm, comprising observation, clinical monitoring, psychosocial support, and QoL assessment.[12]

Patients with a MDS who have symptoms caused by low blood counts are given supportive care to relieve symptoms and improve quality of life. Drug therapy may be used to slow progression of the disease. Certain patients can be cured with aggressive treatment with chemotherapy followed by stem cell transplant using stem cells from a donor.[19]

Central to the management of MDS is best supportive care (transfusion therapy, growth factors, antibiotics) to control the symptoms of bone marrow failure, low-dose standard chemotherapy or immunosuppressive therapies are used for some patients.[8,14,19]

## CURRENT TREATMENT OPTIONS

NICE recommends azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have intermediate-2 and high risk MDS according to the International Prognostic Scoring System (IPSS).[20]

## PLACE OF TECHNOLOGY

If licensed, sabatolimab in addition to azacitidine will offer an additional treatment option for patients with untreated higher risk MDS who currently have few well-tolerated effective therapies available.

# CLINICAL TRIAL INFORMATION

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| **Trial** | **STIMULUS-MDS2*;*** NCT04266301, EudraCT- 2019-002089-11*;* A Randomized, Double-blind, Placebo-controlled Phase III Multi-center Study of Azacitidine With or Without MBG453 for the Treatment of Patients With Intermediate, High or Very High Risk Myelodysplastic Syndrome (MDS) as Per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2)<br>**Phase III** - recruiting<br>**Location(s):** 13 EU countries, UK, Canada, United States and other countries<br>**Primary completion date:** May 2027 |
| **Trial design** | Randomized, parallel assignment, triple-blinded |
| **Population** | N=500; Adult subjects with intermediate, high or very high risk MDS as per IPSS-R, or CMML-2; aged 18 years and over |
| **Intervention(s)** | Sabatolimab (IV) every 4 weeks; a dose of azacitidine (IV) or (SC) |
| **Comparator(s)** | Azacitidine (SC) and placebo (IV) |
| **Outcome(s)** | Overall survival [Time frame: up to 5 years after last patient randomized]<br><br>See trial record for full list of other outcomes. |
| **Results (efficacy)** | - |
| **Results (safety)** | - |

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| **Trial** | **STIMULUS-MDS1*;*** NCT03946670, EudraCT - 2018-004479-11*;* A Randomized, Double-blind, Placebo-controlled Phase II Multi-center Study of Intravenous MBG453 Added to Hypomethylating Agents in Adult Subjects With Intermediate, High or Very High Risk Myelodysplastic Syndrome (MDS) as Per IPSS-R Criteria<br>**Phase II -** active, not recruiting<br>**Location(s):** nine EU countries, UK, Canada, United States and other countries<br>**Primary completion date:** Oct 2023 |
| **Trial design** | Randomized, parallel assignment, triple-blinded |
| **Population** | N=127; Adult subjects with intermediate, high or very high risk MDS as per IPSS-R criteria; aged 18 years and over |
| **Intervention(s)** | Sabatolimab (IV); decitabine (IV); azacitidine (IV) or (SC) |
| **Comparator(s)** | Placebo (IV); decitabine (IV); azacitidine (IV) or (SC) |
| **Outcome(s)** | • Complete remission (CR) rate [Time frame: 7 months after last patient first visit (LPFV)] |

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| | • Progression free survival (PFS) [Time frame: up to 4 years after LPFV]<br><br>See trial record for full list of other outcomes. |
| **Results (efficacy)** | - |
| **Results (safety)** | - |

# ESTIMATED COST

The cost of sabatolimab is not yet known.

Azacitidine 100mg powder for suspension for injection vials is available for £321.00, £272.85, £230.00 or £220.00, depending on the supplier.[21]

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal in development. Pevonedistat with azacitidine for untreated myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (GID-TA10767). Expected publication date: TBC.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

## OTHER GUIDANCE

- British Journal of Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2021.[22]
- European Society for Medical Oncology. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[23]
- London Cancer. Guidelines for the Diagnosis and Management of Adult Myelodysplastic Syndromes. 2015.[24]

# ADDITIONAL INFORMATION

# REFERENCES


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