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Newcastle University

Health Technology Briefing
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Subcutaneous isatuximab with pomalidomide and dexamethasone for treating relapsed and/or refractory multiple myeloma

Company/Developer	Sanofi

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35254	NICE ID: Not available	UKPS ID: 673028

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Subcutaneous isatuximab in addition to pomalidomide and dexamethasone is in clinical development for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM). Multiple myeloma (MM) is a rare, incurable cancer of the plasma cells in the bone marrow. In MM, large amounts of abnormal plasma cells are produced which fill the bone marrow and interfere with the production of other cells, including red and white blood cells and platelets. People with MM will experience periods of time without symptoms followed by periods when the illness comes back ('relapsed' MM). Eventually the periods without symptoms will shorten and the illness will become immune to the drugs ('refractory' MM). New treatments are necessary to prolong overall survival and improve quality of life of patients with this burdensome and incurable disease.

Isatuximab is a monoclonal antibody (a type of protein) that has been designed to attach to the protein CD38, which is found in high amounts on MM cells. By attaching to CD38 on the MM cells, isatuximab activates the immune system (the body's natural defences) to kill the cancer cells. Intravenous (IV) isatuximab in addition to pomalidomide and dexamethasone is already approved for the treatment of adults with RRMM who have received at least two prior therapies. If licensed, subcutaneous (SC) isatuximab in combination with pomalidomide and dexamethasone, would offer an additional treatment option for RRMM patients who have received at least one prior line of therapy.

Proposed Indication

For the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor.[1]

Technology

Description

Isatuximab (SAR650984) is an immunoglobulin G (IgG) 1 monoclonal antibody that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation 38 (CD38). CD38 is expressed in a number of haematological malignancies, including multiple myeloma (MM). Isatuximab has been found to kill tumour cells via multiple biological mechanisms.[2] In vitro, isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Furthermore, isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism. In vitro, isatuximab blocks the enzymatic activity of CD38 which catalyses the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), a calcium mobilizing agent. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in multiple myeloma cells.[3]

Isatuximab, in addition to pomalidomide and dexamethasone, is in clinical development for the treatment of adult patients with RRMM who have received at least 1 prior line of therapy, including lenalidomide and a proteasome inhibitor. In the phase III clinical trial (NCT05405166), subcutaneous isatuximab is administered weekly for 4 weeks during cycle 1 (days 1, 8, 15, and 22) and day 1 and 15 of subsequent cycles (each cycle will be 28 days in duration), in combination with pomalidomide (oral) taken on day 1 to day 21 of each cycle prior to or after isatuximab administration, and dexamethasone (oral) on day 1, 8, 15 and 22, until disease progression, unacceptable adverse events, or participant request to discontinue therapy.[1]

Key Innovation

Patients with RRMM experience several relapses and become refractory to successive therapies. These patients experience decreasing duration of response and poor overall survival with successive lines of therapy. Consequently, the number of previous lines of therapy and the types of agents that a patient has received are important considerations when determining treatment sequencing. In a previous phase 3 study (NCT02990338), isatuximab in addition to pomalidomide and dexamethasone improved progression-free survival and overall response rate regardless of prior lines of therapy or refractory status, consistent with the benefit in the overall population.[4] Subcutaneous delivery of isatuximab allows for a shorter duration of administration (within several minutes) compared with the intravenous (IV) route, optimising convenience of administration and healthcare resources and enhancing comfort and quality of life of patients.[5]

If licensed, subcutaneous isatuximab combined with pomalidomide and dexamethasone will offer a new second-line treatment option for patients with RRMM who have received prior treatment with lenalidomide and a proteasome inhibitor. [6]

Regulatory & Development Status

IV formulation of isatuximab has Marketing Authorisation in the EU/UK for the following indications:[3]

- in combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy.

IV Isatuximab in addition to pomalidomide and dexamethasone is also in the phase II clinical development for AL Amyloidosis.[7]

IV Isatuximab has been granted an orphan designation in the EU in 2014 for the treatment of plasma cell myeloma.[8]

Patient Group

Disease Area and Clinical Need

MM is a plasma cell (PC) dyscrasia that is characterised by the uncontrolled proliferation of malignant PCs within the bone marrow, as well as clinical symptoms, such as bone destruction, kidney injury, and paraproteinemia.[9] Relapsed or refractory MM is defined as a disease which becomes non-responsive or progressive while the patient is on salvage therapy or within 60 days of the last treatment in patients who had achieved a minimal response or better on prior therapy. The genomic complexity and clonal evolution of MM over the course of treatment are thought to contribute to drug resistance and disease progression.[10] The cause of MM is unknown but is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS) which is characterised by an excess number of protein molecules (immunoglobulins) present in the blood. Estimates suggest approximately 1 in every 100 people with MGUS go on to develop MM on an annual basis.[11] Additional risk factors for MM include age, gender, and ethnicity. Cases affecting those under 40 years of age are rare, with men more likely to develop the disease than women. The symptoms of MM can include bone pain (notably in the spine, hips or chest), nausea, constipation, loss of appetite, physical and mental fatigue, frequent infections, reduced kidney function, anaemia, weight loss, loss of muscle control in the lower extremities, and excessive thirst.[12] MM patients experience a variety of disease-related events and subsequent disability, such as bone destruction leading to pain, height reduction and body shape changes, bone marrow failure, renal failure, immunodeficiency, and the psychosocial burden of a diagnosis of cancer.[13]

There are around 5,951 new MM cases in the UK every year, that's about 16 every day (2016-2018). Myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018). In females in the UK, myeloma is the 18th most common cancer, with around 2,500 new cases every year (2016-2018). In males in the UK, myeloma is the 16th most common cancer, with around 3,400 new cases every year (2016-2018). Each year more than 4 in 10 (43%) of all new myeloma cases in the UK are diagnosed in people aged 75 and over (2016-2018). Myeloma incidence rates are projected to rise by less than 1% in the UK between 2023-2025 and 2038-2040. The survival rate of myeloma for 10 or more years is 29% (2013-2017). 3,098 deaths has been reported from myeloma (2017-2019).[14] In England in 2022-2023, there were 155,822 finished consultant episodes (FCE), and 150,740 hospital admissions for multiple myeloma (ICD-10 code C900), resulting in 99,552 FCE bed days and 142,557 day cases.[15]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following regimen for the treatment of RRMM:[16-18]

- Daratumumab monotherapy
- Ixazomib with lenalidomide and dexamethasone
- Isatuximab with pomalidomide and dexamethasone

Clinical Trial Information	
Trial	NCT05405166, 2021-002485-41; A Randomized, Phase 3, Open Label Study Evaluating Subcutaneous Versus Intravenous Administration of Isatuximab in Combination With Pomalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma (RRMM) **Phase III –** Recruiting **Location(s):** Ten EU countries, UK, USA, Canada, and other countries **Primary completion date:** May 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=534 (estimated); aged 18 years and older; participants with MM who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor
Intervention(s)	Isatuximab (SC) weekly for 4 weeks during cycle 1 (days 1, 8, 15, and 22) and day 1 and 15 of subsequent cycles + pomalidomide (oral) on day 1 to day 21 of each cycle prior to or after isatuximab administration + dexamethasone (oral) on day 1, 8, 15 and 22 (to be repeated every 28 days)
Comparator(s)	Isatuximab (IV) weekly for 4 weeks during cycle 1 (days 1, 8, 15, and 22) and day 1 and 15 of subsequent cycles + pomalidomide (oral) on day 1 to day 21 of each cycle prior to or after isatuximab administration + dexamethasone (oral) on day 1, 8, 15 and 22 (to be repeated every 28 days)
Outcome(s)	Primary outcome measures: • Overall response rate (ORR) [Time Frame: Up to approximately 2 years] • Observed concentration before dosing (Cthrough) at steady state [Time Frame: Predose at Cycle 6 Day 1 (duration of each cycle is 28 days)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04045795, A Multi-centre, Open-label, Phase 1b Study to Assess the Pharmacokinetics, Safety, and Efficacy of Subcutaneous and Intravenous Isatuximab (SAR650984) in Combination With Pomalidomide and Dexamethasone, in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) **Phase I** – Active, not recruiting.

	Location(s): Three EU countries, USA and other countries **Primary completion date**: February 2024
Trial Design	Randomised, sequential assignment, open label
Population	N=56 (actual); aged 18 years and older; participants previously diagnosed with MM and currently require treatment because MM has relapsed following a response, and have received at least two previous therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on last therapy or after completion of the last therapy
Intervention(s)	• Isatuximab (SC) dose level 1 once weekly for 4 weeks (cycle 1) and on day 1 and day 15 of each subsequent cycle + pomalidomide (oral) + dexamethasone (oral) • Isatuximab (SC) dose level 2 once weekly for 4 weeks (cycle 1) and on day 1 and day 15 of each subsequent cycle + pomalidomide (oral) + dexamethasone (oral) • Isatuximab (SC) dose level 3 using the investigational injector device once weekly for 4 weeks (cycle 1) and on day 1 and day 15 of each subsequent cycle + pomalidomide (oral) + dexamethasone (oral) • Isatuximab (IV) once weekly for 4 weeks (cycle 1) and on day 1 and day 15 of each subsequent cycle + pomalidomide (oral) + dexamethasone (oral) • Isatuximab (IV) once weekly for 4 weeks (cycle 1) and on day 1 and day 15 of each subsequent cycle + pomalidomide (oral) + dexamethasone (oral)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Assessment of adverse events (AES) [Time Frame: Baseline to 30 days after last study treatment administration (up to approximately 14 months after first study treatment administration)] • Pharmacokinetic (PK) assessment: Ceoi [Time Frame: Baseline to end of treatment (EOT) after Isatuximab SC and to Cycle 10 after IV (28 days per Cycle)] • PK assessment: Cmax [Time Frame: Baseline to EOT after Isatuximab SC and to Cycle 10 after IV (28 days per Cycle)] See trial record for full list of other outcomes.
Results (efficacy)	At study entry, 67% of IV, 33% of IP (infusion pump) 1000, 60% of IP1400, and 50% of OBDS (on-body delivery system) patients had International Staging System stage II-III disease, and ≥50% of patients in each cohort had received ≥3 prior LOT (lines of treatment). 50% of IV patients were refractory to immunomodulatory drugs and proteasome inhibitors, as well as 66.7% of IP1000, 40% of IP1400 and 72.7% of OBDS cohorts, respectively. ORR (overall response rate) in patients treated at the RP2D (recommended phase 2 dose) was 75.0%, and 66.7% in the IV and IP1000 cohorts.[5]

Results (safety)	Treatment-related G3-4 treatment emergent adverse events (TEAE) occurred in 91.7% patients of the IP1000 cohort and approximately 80% in the IV, IP1400 and OBDS cohorts. Serious treatment related TEAEs occurred in 16.7% patients of the IV, 25% in the IP1000, 50% in the IP1400 and 13.6% in the OBDS cohort. Isatuximab administration was well tolerated, with infrequent infusion reactions (Irs) (≤10% in each cohort, all G2), only at first administration, and none in the OBDS cohort. The median duration of OBDS injections was 10 min, and all injections were successfully completed with no interruption. There was good local tolerability: 5 (22.7%) patients experienced 7 injection site reactions, all G1, out of 404 administrations (1.73%), including 5 injection site erythema, 1 injection site haemorrhage, and 1 injection site induration. Grade ≥3 laboratory neutropenia was observed in 83% of IV patients and ~90% of SC patients, OBDS and IP. Febrile neutropenia occurred in 1 (4.5%) patient in the IV, 2 (20%) patients in the IP1400 and 1 (4.5%) in the OBDS cohorts.[5]

Estimated Cost

IV Isatuximab is already marketed in the UK:[19]

- 100mg/5ml vial costs £506.94
- 500mg/25ml vial costs £2,534.69

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies (ID4026). Expected: February 2024.
- NICE technology appraisal in development. Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma [ID3797]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments [ID6193]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ciltacabtagene autoleucel for treating relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 therapies (ID4012). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax with dexamethasone for treating relapsed or refractory (11;14)-positive multiple myeloma after lenalidomide and a proteasome inhibitor [ID4040]. Expected date of issue to be confirmed.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA870). February 2023.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA123). April 2022.
- NICE technology appraisal. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658). November 2020.
- NICE clinical guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Bendamustine for relapsed multiple myeloma (all ages). 2020. 200604/P.
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Other Guidance

- European Medicines Agency. Guideline on the New treatment option for heavily pre-treated multiple myeloma patients. October 2023.[20]
- British Society for Haematology (BSH) and the UK Myeloma Forum (UKMF). Guidelines on the diagnosis, investigation, and initial treatment of myeloma. 2021.[21]
- European Society of Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2021.[22]
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