NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
June 2024

Resminostat for maintenance treatment of patients with advanced stage mycosis fungoides or Sézary syndrome

Company/Developer	4SC AG

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 37642	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Resminostat is in clinical development for the maintenance treatment of adults with mycosis fungoides (MF) and Sézary syndrome (SS) which are the most common types of cutaneous T-cell lymphoma (CTCL), a rare type of non-Hodgkin lymphoma affecting the skin. CTCL can develop when T-cells become abnormal. T-cells are one of the important types of white blood cells in the immune system and play a central role in the adaptive immune response. MF is usually a very slow-growing type of lymphoma that primarily affects the skin. It arises from malignant T-cells that infiltrate the top two layers of the skin (epidermis and dermis). SS usually grows faster and involves the uncontrolled growth of cancerous T-cells that spread through the bloodstream. CTCL may cause skin changes, including rash-like patches, itchy and sometimes painful areas, plaques, and lumps. MF and SS are often challenging to manage due to the lack of reliably curative therapies and the necessity for ongoing treatment and symptom control.

Resminostat is a medication currently being studied for the treatment of adults with MF and SS. It is typically administered orally in the form of tablets. Resminostat can delay disease progression in advanced CTCL and improve progression-free survival. It also reduces the risk and improves the average time until the next treatment. If licensed, it could offer improved outcomes with a favourable safety profile for patients with advanced MF and SS.

Proposed Indication

Treatment of advanced stage (IIB-IVB) mycosis fungoides (MF) or Sézary syndrome (SS) in adults patients who have achieved disease control with systemic therapy.[1]

Technology

Description

Resminostat (4SC-201)[1] is an inhibitor of class I, IIb and IV histone deacetylases (HDACs), including pronounced activity against HDAC6.[2] HDACs are enzymes responsible for removing acetyl groups from lysine residues on proteins, including histones. By inhibiting HDACs, resminostat prevents the removal of acetyl groups from lysine residues. This changes gene expression levels in tumour cells and deregulates pathways involved in cell differentiation, such as WNT signalling. Changes in cell differentiation are very often the cause of tumour progression, metastasis and acquired resistance to anti-cancer treatment.[3] In cutaneous T-cell lymphoma (CTCL) cell lines, resminostat upregulates the expression of Th1 and reduced Th2 lineage-associated genes. An imbalance between Th1 and Th2 cells is considered to contribute to pathogenesis of CTCL; increased expression of Th2-related genes is especially associated with disease progression. This indicates potential as a maintenance therapy as well as treating progressive disease. In addition, resminostat increases the immunogenicity of tumours by enhancing natural killer cell recognition and killing, increasing expression and presentation of tumour-associated antigens that support T-cell functions, and reducing non-specific immunosuppressive mechanisms.[2,4]

Resminostat is currently in clinical development for the maintenance treatment of advanced stage MF or SS in adults. In the phase II clinical trial NCT02953301, adults aged 18 years and older were orally administered resminostat at a dose of 3 x 200 mg tablets for five days followed by nine days rest (cycles continued until progress or unacceptable toxicity).[1]

Key Innovation

Resminostat is the only proven maintenance therapy for CTCL, offering significant benefits for patients who would otherwise have no other similar treatment options available to them. Favourable pharmacokinetic properties with satisfactory target modulation were confirmed, and signs of clinical activity were elicited with the use of resminostat as monotherapy.[5] Maintenance treatment is a unique and innovative approach in CTCL. The goal is to prolong the period during which patients remain stable and do not experience disease progression. CTCL is not curable and treatment options for advanced-stage CTCL are limited. The duration of patients' response to the available treatment options is often short-lived and declines as the severity of the disease increases. The key therapeutic challenge in advanced-stage CTCL is therefore to make remissions more durable by halting disease progression and improving patient's quality of life. [6] Resminostat inhibits proliferation of a large variety of rodent and human cancer cell lines at sub-to-low micromolar concentrations.[7]

Resminostat was well tolerated when used as a single agent at doses associated with therapeutically relevant plasma concentrations, with evidence of antitumour activity. Furthermore, if licensed, resminostat will offer a unique innovative treatment approach in MF and SS intended to prolong the period patients are stable and not progressing. Resminostat did not show any major, dose-limiting hematologic toxicity at the dose levels assessed and has the potential to be used in combination with myelosuppressive anticancer agents. Side effects of Resminostat are mainly mild to moderate, as well as being reversible and manageable. [7,8]

Regulatory & Development Status

Resminostat does not currently have marketing authorisation in the EU/UK for any indication.

Resminostat is also in the phase III/II clinical development for the following indications:[9]

- Relapsed or refractory Hodgkin's lymphoma
- Advanced hepatocellular carcinoma
- Advanced colorectal carcinoma

Patient Group

Disease Area and Clinical Need

Conceptually, MF and SS, as the most common types of CTCL, are classified as distinct entities arising from different T helper cell subsets. T-cell skin lymphoma is more common in older adults and the average age at diagnosis is 55 years. Men are around twice as likely to develop T-cell skin lymphoma than women.[10] MF presents clinically with patch, plaque and/or tumour stages, but can also evolve as erythroderma, which in turn is pathognomonic for SS. SS is characterized by a detectable tumour cell burden (Sézary cells) in the peripheral blood, which is consistent with advanced stage disease and a poor prognosis. In early stage of MF, which is the predominant form, the prognosis is generally favourable. However, in up to 30% of patients there is progression of skin lesions, which can ultimately lead to visceral involvement. The histological manifestation of MF can be subtle in the early stage and therefore a careful clinicopathological investigation is paramount.[11,12] The precise cause of MF and SS remains unclear, though several factors may be considered as potential risk factors, including aging, gender (particularly being male), compromised immune system function (such as from AIDS or an organ transplant), and certain infections like the Epstein-Barr virus.[13]

In England (2017), there were 12,065 patients diagnosed with non-Hodgkin lymphoma. This means almost 50 people are diagnosed with non-Hodgkin lymphoma every day in the UK.[14] The annual incidence of CTCL in the UK is 0.7 per 100,000 people. MF and SS have been found to represent 55% and 2.5% of CTCLs, respectively, which means the annual incidence of MF/SS is 0.4 per 100,000 people. In the early stages of the disease, patients with either MF or SS have a median survival of 21.5 years from diagnosis. This reduces drastically to 1.4 to 6 years for advanced patients (Stage IIB-IV MF and SS) depending on stage and disease typology (MF vs SS). [15] In England in 2022-2023, there were 419 and 692 finished consultant episodes (FCE) and 364 and 686 hospital admissions for MF and SS (ICD-10 codes C84.0 and C84.1), resulting in 998 and 435 FCE bed days and 310 and 510 day cases for each respective condition.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following regimen for the treatment of advanced stage MF or SS:[17]

- Mogamulizumab is recommended, within its marketing authorisation, as an option for treating Sézary syndrome in adults who have had at least one systemic treatment.
- Mogamulizumab is recommended as an option for treating mycosis fungoides in adults, only if:
    - their condition is stage 2B or above and
    - they have had at least 2 systemic treatments and
    - the company provides mogamulizumab according to the commercial arrangement.
- Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

Clinical Trial Information

Trial	**RESMAIN**, NCT02953301, 2016-000807-99; A Multicentre, Double Blind, Randomised, Placebo-controlled, phase II trial to evaluate resminostat for maintenance treatment of patients with advanced stage (stage IIB-IVB) MF or SS that have achieved disease control with systemic therapy **Phase II:** Active, not recruiting **Location(s):** Nine EU countries, UK, Japan and Switzerland **Primary completion date:** March 2023
Trial Design	Randomised, multicentre, triple blind, placebo-controlled
Population	N=201 (actual); subjects with histologically confirmed MF (stage IIB-IVB) or SS after at least one prior systemic therapy or TSEB; aged 18 years and older
Intervention(s)	Resminostat 3 x 200 mg tablets taken orally; five days treatment followed by nine days rest (cycles until progress or unacceptable toxicity)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: progression-free survival [Time frame: from date of randomization until first documented progression or date of death from any cause, whichever came first, up to approximately 32 months]. See trial record for full list of other outcomes.
Results (efficacy)	Resminostat showed a statistically significant improvement in PFS of 97.6% compared to placebo, with a risk reduction of 38% (median PFS: 8.3 months versus 4.2 months; p=0.015; hazard ratio (HR): 0.623 (95% confidence interval (CI): 0.424, 0.916). Resminostat median TTNT versus placebo showed a significant improvement, more than doubling to 8.8 months compared to 4.2 months; p= 0.002; HR: 594 (95% CI: 0.424, 0.916). Additional analyses showed a clinically meaningful improvement in median "total" PFS (defined from start of last prior therapy to disease progression) of 24.3 months for patients treated with resminostat, compared to 14.9 months for those in the placebo group.[18]
Results (safety)	Side effects were mainly mild to moderate, reversible, and manageable.[18]

Estimated Cost

The cost of resminostat is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome (TA754). December 2021.
- NICE technology appraisal guidance. Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma (TA577). April 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical commissioning policy: Bendamustine with rituximab for first line treatment of advanced indolent non-Hodgkin's lymphoma (all ages). 170055P. June 2018.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update. 2023.[19]
- Dippel E, Assaf C, Becker JC, et al. S2k-Guidelines – Cutaneous lymphomas (ICD10 C82 - C86): Update. 2022.[20]
- European Society for Medical Oncology. EHA/ESMO Clinical Practice Guidelines for the British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas. 2018.[21]

Additional Information

4SC AG did not enter information about this technology onto the UK PharmaScan database, the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.