National Institute for Health Research

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Synthetic hypericin (SGX301; VIMRxyn) for cutaneous T-cell lymphoma, unspecified

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LAY SUMMARY

Cutaneous T-cell lymphoma (CTCL) is a rare type of non-Hodgkin lymphoma that affects the skin. It is caused by white cells, called lymphocytes, growing in an uncontrolled way. CTCL usually develops very slowly and at an early stage topical treatments of the localised accumulation of the cancer are usually used. At a later, more advanced stage, systemic treatments may be used (these work throughout the body as the cancer spreads outside of the skin).

In the UK, the annual incidence of cutaneous T-cell lymphoma is 0.27 per 100,000 population. It is more common in older male adults. If treated at an early stage the chances of surviving after five and ten years are very high. Disease progression is also very low in the earlier stages of the disease.

Synthetic hypericin (SGX301) is a new investigational drug that can be safely applied directly on the affected skin. It reacts to fluorescent light, killing the cancer cells. This drug may avoid the use of alternative treatments that may cause skin cancer in patients exposed to them.

TARGET GROUP

Cutaneous T-cell lymphoma (CTCL), unspecified.

TECHNOLOGY

DESCRIPTION

Synthetic hypericin (SGX301) is a novel, first-in-class photodynamic therapy. Using a potent photosensitizer, synthetic hypericin is topically applied and activated by safe visible fluorescent light. This treatment avoids the risk of secondary malignancies (including melanoma) inherent with the frequently employed DNA-damaging chemotherapeutic drugs and other photodynamic therapies that are dependent on ultraviolet A (UVA) light exposure.

It will be available as an ointment to be applied onto the skin lesions of patients with CTCL and the drug is actively taken up by the cancerous T-cells, substantially more than the healthy tissue cells. With visible spectrum light, hypericin is activated and reacts with oxygen in skin cells to create toxic molecules containing oxygen called 'reactive oxygen species', which are expected to kill the cancer cells.

Topical, synthetic hypericin has demonstrated safety in a phase I clinical study in healthy volunteers. In a phase II, placebo-controlled, randomised, double-blind clinical study in patients with CTCL, topical application of hypericin demonstrated a response in 58.3% of patients compared with 8.3% patients treated with placebo ($p \leq 0.04$).[1,2]

Currently recruiting, the phase III trial (NCT02448381) participants will be administered 0.25% synthetic hypericin (SGX301) in USP Hydrophilic Ointment applied twice per week, covered by opaque bandage for 12-24 hours, then treated with an initial dose of 5 J/cm^2 fluorescent light. Three treatment cycles, each six weeks followed by a two week rest period are planned. [3]

Synthetic hypericin (SGX301) does not currently have marketing authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, synthetic hypericin (SGX301) will offer an additional treatment for CTCL. Clinical studies suggest that this technology might be of significant benefit as a first-line treatment for patients with early stage CTCL. [4]

DEVELOPER

Soligenix, Inc.

AVAILABILITY, LAUNCH or MARKETING

Synthetic hypericin (SGX301) has received the following designations:

- orphan drug designation in the EU for 2015; [4]

- Promising Innovative Medicine (PIM) designation from the UK Medicines and Healthcare Products Regulatory Agency in 2017; [5]
- orphan drug designation in the US in 2000. [6]

There is no available information on anticipated submission plans for marketing authorisation in the EU or UK. The phase III trial is expected to complete final data collection for the primary outcome measure in the USA in December 2017. [3] Long-term follow-up continues for 6 months after treatment ends.[a]

PATIENT GROUP

BACKGROUND

Non-Hodgkin's lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout the body.[7] CTCL is a rare type of non-Hodgkin's lymphoma (NHL) that affects the skin. It is caused by the uncontrolled growth of cancerous T-lymphocytes. [8] Many types of CTCL start as flat red patches (tumours) on the skin, which may be itchy and sometimes painful. [9] Some people with CTCL experience swelling of the lymph nodes. Early stage CTCL is typically indolent; some patients with early-stage CTCL do not progress to later stages at all, while others progress rapidly, with the cancer spreading to lymph nodes and/or internal organs. [10]

The most common subtype of CTCL is mycosis fungoides (MF), which affects around half of those diagnosed with CTCL. [10] Starting as an irregular shaped area of dry or scaly skin, MF is a very slow growing (low grade) form of CTCL. Patches may appear anywhere on the body but are commonly found on the chest, abdomen, back and buttocks. These abnormal areas of scaly, red skin, called patches, in some patients may progress to form scaly raised patches, called plaques.[8] In a small number of people, raised lumps (tumours) may appear. In rare advanced cases of the disease, the skin appears red, swollen and sore all over, and is termed erythrodermic mycosis fungoides.

Sézary syndrome (SS) is a less frequent erythrodermic variant of CTCL with leukaemic involvement. [11] SS occurs in about 3% of patients with CTCL and is diagnosed by the presence of Sézary cells (malignant T cells with cerebriform nuclei) in the blood in addition to erythroderma. [12] Patients present with bright red skin that is usually pruritic. They often have fine scaling with thickened, scaly, and fissured palms and soles. [13]

CLINICAL NEED and BURDEN OF DISEASE

The annual UK incidence of cutaneous lymphoma is around 0.4 per 100,000 population, and approximately 66% of cutaneous lymphomas are of T-cell origin (CTCL) (approximately 0.27 per 100,000 population). [14,15]

Around 6 out of 10 people (60%) diagnosed with non-Hodgkin's lymphoma are aged 65 and over. Non-Hodgkin's lymphoma is slightly more common in men than in women.[14]

The latest Hospital Episodes Statistics (2015-2016) recorded 4,611 finished consultant episodes for a primary diagnosis of Mature T/NK-cell lymphoma whereby a total of 245 final consultant episodes were recorded for CTCL and 221 cases required admission to hospital. [16]

[a] Information provided by company.

According to the British Association of Dermatologists 2003 guidelines, the prognosis in cutaneous T-cell lymphoma varies greatly depending on the stage of the disease. The overall survival rate at five years ranges between 96 to 100% in patients at stage IA, to 0 to 15 % in those at the last stage IVB. Prognosis of disease progression for patients diagnosed at initial stage (stage IA) is 4% at five years, the disease progresses more rapidly in those patients at later stages (100% for stage IVB). [15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nelarabine for treating refractory T-cell lymphoblastic non-Hodgkin's lymphoma (GID-TA10087).
- NICE technology appraisal in development. Lymphoma (non Hodgkin's, peripheral T-cell) - pralatrexate (GID-TAG424).
- NICE technology appraisal in development. T-cell lymphoma (peripheral, relapsed or refractory) – romidepsin (GID-TAG433).
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016
- NICE diagnostics guidance. VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions (DG19). November 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Improving Outcomes: A Strategy for Cancer (2011).
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for haematopoietic stem cell transplantation (Adult). B04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/S/b.

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Primary cutaneous lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2013. [17]
- European Organisation for Research and Treatment of Cancer (EORTC). EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. 2006. [18]
- British Association of Dermatologists. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas (update in progress). 2003. [15]

CURRENT TREATMENT OPTIONS

The British Association of Dermatologists published guidelines for the management of primary cutaneous T-cell lymphomas in 2003. These guidelines have been accredited by NICE and are currently in the process of being updated. [15]

In summary, treatments for CTCL can be divided into topical (applied to the skin) and systemic (affecting the whole body):

- topical treatments include topical corticosteroids; topical chemotherapy (drug called carmustine); ultraviolet light (PUVA) taken in combination with psoralen (tablets) or narrow band UVD treatment (TLO-1);
- systemic treatments include cytotoxic medicines; low dose radiotherapy to the skin; total skin electron beam therapy (TSEBT); interferon alfa; bexarotene (monotherapy or in combination with PUVA, interferon or extracorporeal photopheresis); extracorporeal photopheresis (ECP) or stem cell or bone marrow transplant. [4]

EFFICACY and SAFETY

Trial	**FLASH; NCT02448381**
Sponsor	Soligenix
Status	Ongoing, currently recruiting
Source of Information	Trial registry [3]
Location	US
Design	Randomised, placebo-controlled, double-blind
Participants	N=120 (estimated); 18 years and older with clinical diagnosis of CTCL (mycosis fungoides) Stage IA, Stage IB, or Stage IIA.
Schedule	0.25% SGX301 in USP Hydrophilic Ointment applied twice per week, covered by opaque bandage for 12-24 hours, then treated with an initial dose of 5 J/cm^2 fluorescent light. 6-week course.
Follow-up	Not reported
Primary Outcomes	Treatment Response in 3 treated lesions as defined as a ≥50% improvement in the Composite Assessment of Index Lesion Disease Severity (CAILS).
Secondary Outcomes	Complete response; degree of improvement; duration of response as measured monthly for 6 months; time to relapse; safety.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Final data collection date for primary outcome measure reported as December 2017.

ESTIMATED COST and IMPACT

COST

The cost of synthetic hypericin (SGX301) is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival	☒ Reduced symptoms or disability
☐ Other	☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services	☐ Decreased use of existing services
☐ Re-organisation of existing services	☐ Need for new services
☐ Other	☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs	☐ Reduced drug treatment costs
☐ Other increase in costs	☐ Other reduction in costs
☒ Other	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

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