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HEALTH TECHNOLOGY BRIEFING
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Topical sirolimus for angiofibroma in tuberous sclerosis complex

NIHRIO ID	17160	**NICE ID**	9863
Developer/Company	Nobelpharma Co Ltd	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Topical sirolimus is in clinical development for tuberous sclerosis complex (TSC). TSC is a rare genetic multisystem disorder that is typically apparent shortly after birth. TSC is caused by a mutation (change to genetic material) in one of two different genes (TSC1 or TSC2). Small bumps or red spots, known as angiofibroma, may appear between the ages of 3 and 5 years, primarily on the face. Angiofibromas are benign proliferations that can cause significant disfigurement and bleeding without an effective treatment. Current treatments for angiofibroma are invasive, such as surgery or laser treatment, which are difficult to administer to young children or patients with developmental disabilities. These treatments, can also cause relapse, change of pigment, scar and risk of infection.

Topical sirolimus is an immunosuppressant. It inhibits the activity of mTOR (mammalian target of rapamycin), where overactivation of mTOR promotes angiogenesis. Topical treatment means that sirolimus is applied to the skin and is therefore less invasive. If licenced, topical sirolimus will offer as an additional treatment option for patients with angiofibroma due to TSC.

PROPOSED INDICATION

Topical Sirolimus is indicated for the treatment of angiofibroma in children and adults aged 3 years and older associated with tuberous sclerosis complex (TSC) .[1]

TECHNOLOGY

DESCRIPTION

Sirolimus (Rapamune, NPC-12G, Opsiria, DE-109, Rapalimus gel, topical rapamycin) is an immunosuppressant.[2-4] Sirolimus belongs to a novel class of anti-cancer drugs called as mTOR (mammalian target of rapamycin) inhibitors.[4] A germline mutation of the TSC1 or TSC2 gene, leading to activation of the mammalian target of rapamycin (mTOR) pathway, accounts for the pathogenesis of TSC-associated angiofibromas. Activated mTOR subsequently activates p70 ribosomal protein S6 kinase (p70S6K) and ribosomal protein S6 (S6) by phosphorylation.[5] Sirolimus binds to FKBP12 (FK506-binding protein) to form a complex, which inhibits mTOR activation.[6]

In the phase III trial (NCT02634931) sirolimus (0.2%) is administered topically twice a day for 52 weeks or longer.[7] In the phase III clinical trial (NCT02635789), topical sirolimus (0.2%) is administered twice a day for 12 weeks.[1]

INNOVATION AND/OR ADVANTAGES

As current treatments are invasive, such as surgery or laser treatment are difficult to administer to young children or patients with developmental disabilities, no treatment is given to patients until the condition became serious.[8] These treatments can also cause relapse, change of pigment, scar and risk of infection.[9]

The effectiveness of topical sirolimus for the treatment of skin lesions accompanying TSC has been made clear in academia. A research group at Osaka University who were investigating the indication of topical sirolimus conducted clinical trials and found that topical sirolimus was extremely effective as an external gel on skin lesions accompanying TSC.[10]

For the NCT02635789 clinical trial, topical sirolimus (0.2%) demonstrated a significant clinical benefit for patients with TSC involving angiofibroma, thus providing a promising therapeutic modality.[11]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Topical sirolimus currently has no regulatory designation in the UK or EU. Market authorisation has been filed for the United States (December 2020).[3] Sirolimus was awarded orphan designation (EU/3/17/1886) for the treatment of tuberous sclerosis in June 2017.[12]

Topical sirolimus is currently in several phase II/III clinical trials, including for the treatment of cutaneous lymphatic malformations and epidermolysis bullous simplex.[13]

PATIENT GROUP

DISEASE BACKGROUND

TSC is an autosomal dominant genetic disorder caused by *TSC1* or *TSC2* mutations, which is characterised by hamartomas (benign lesions composed of aberrant disorganized growth of mature tissues) in various organs (e.g., skin, brain, and kidneys).[14,15] TSC provokes skin lesions (e.g., hypomelanotic macules, angiofibromas, and cephalic plaques), epilepsy, neurodevelopmental disorders, and other clinical manifestations. Regarding skin lesions, hypomelanotic macules (white or lighter patches of skin that may appear anywhere on the body and are caused by a lack of melanin) develop at birth or later in the majority of affected newborns.[14,16] Facial angiofibromas usually appear by age 5 and gradually proliferate thereafter. Facial skin lesions deteriorate as TSC progresses on a yearly basis, which adversely affects the quality of life of patients by causing psychologic and social distress.[14]

In around 3 in every 4 cases, the genetic fault occurs for no apparent reason in people without any other affected family members. In the remaining 1 in 4 cases, the fault is passed on to a child by their parents. Only one parent needs to carry the faulty gene to pass it on, and a parent who has one of the faulty genes has a 1 in 2 chance of passing it on to each child they have. The parent carrying the faulty gene will also have tuberous sclerosis, although sometimes it may be so mild, they do not realise.[17]

CLINICAL NEED AND BURDEN OF DISEASE

TSC is a rare genetic disorder that effects approximately 1 in 25,000 to 1 in 11,300 new-borns in Europe. Males and females are affected in equal numbers and the disorder occurs in all races and ethnic groups.[18]

Using the 1987 to 2013 data from the Clinical Practice Research Datalink (CPRD) linked to secondary data from the Hospital Episodes Statistics (CPRD-HES) database, 334 patients out of approximately 15.5 million patients had a recorded diagnosis of TSC.[19]

Between 1981 and 2015, 284 patients attended the Bath TSC clinic. 16 patients were identified to have died from TSC complications, where the median age of death was 33 years and the most common cause of mortality in TSC was renal disease.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

TSC is a lifelong condition that requires long-term care and support from a range of different healthcare professionals.[21] Paediatricians and general internists, neurologists, dermatologists, cardiologists, dental specialists, eye specialists, psychiatrists, and other healthcare professionals may need to systematically and comprehensively plan an affected child's treatment. Genetic counselling will be of benefit for affected individuals and their families.[18]

The non-pharmacological treatment option for angiofibroma in TSC include laser therapy, which can be used to improve the appearance of the skin if necessary. If the growths or

patches return, repeated laser therapy may be required. Using sun cream is also important to protect the skin.[21]

CURRENT TREATMENT OPTIONS

Currently, there is no cure for TSC.[17] Abnormal growths or patches of skin don't usually present a serious health problem, but their appearance can affect a person's confidence and self-esteem. Research has shown the effectiveness of topical mTOR inhibitor in treating skin abnormalities caused by tuberous sclerosis. The rash also usually shows significant improvement in those taking mTOR inhibitors as tablets for their kidneys or brain tumours.[21]

PLACE OF TECHNOLOGY

If licenced, topical sirolimus will offer an additional treatment option for children and adults aged 3 years and older with angiofibroma due to TSC.

CLINICAL TRIAL INFORMATION

Trial	**NCT02634931;** A Long-term, Single-arm, Open-label Trial of NPC-12G (Topical Formulation of Sirolimus) to Angiofibroma and Other Skin Lesions in Patients With Tuberous Sclerosis Complex **Phase III** - Completed **Location(s):** Japan **Study completion date:** October 2018
Trial design	Single-arm, open-label, multicentred.
Population	N = 94, patients aged 3 years old or greater, patients who are diagnosed as definite diagnosis according to diagnostic criteria for tuberous sclerosis complex, patients with skin lesions such as angiofibroma, white macules or plaque upper neck associated with tuberous sclerosis complex at the screening visit or the baseline visit.
Intervention(s)	Sirolimus gel is administered topically twice a day for 52 weeks or longer.
Comparator(s)	-
Outcome(s)	Primary Outcome(s): The discontinuation rate due to adverse events [Time Frame: 52 weeks and longer] See trial record for full list of other outcomes.
Results (efficacy)	At 52 weeks, the response rates of angiofibromas were 78.2% [95% confidence interval (CI) 68.0–86.3%].[14]
Results (safety)	Among 94 enrolled patients (mean age, 21 years; range 3–53 years), the rate of adverse event-caused (AE-caused) discontinuation was 2.1% (2/94 patients). Although application site irritation and dry skin occurred relatively frequently, none of the drug-related AEs were serious; most

	of the drug-related AEs resolved rapidly. The major drug-related AEs (⩾ 5% in incidence) were application site irritation (30.9%), dry skin (27.7%), acne (20.2%), eye irritation (8.5%), pruritus (8.5%), erythema (7.4%), dermatitis acneiform (6.4%), and dermatitis contact (5.3%).[14]

Trial	**NCT02635789;** A Double-blind, Randomized, Placebo-controlled Phase III Trial to Investigate the Efficacy and Safety of NPC-12G Gel (Topical Formulation of Sirolimus) to Angiofibroma and Other Skin Lesions in Patients With Tuberous Sclerosis Complex **Phase III** - Completed **Location(s):** Japan **Study completion date:** October 2016
Trial design	Double-blind, quadruple-masking, randomised, placebo-controlled, parallel assignment.
Population	N = 62, patients aged 3 years old or greater, patients who are diagnosed as definite diagnosis according to diagnostic criteria for tuberous sclerosis complex, patients with three or more papules of angiofibroma (>= 2 mm in diameter with redness in each) on the face at screening tests.
Intervention(s)	Sirolimus gel is administered topically twice a day for 12 weeks.
Comparator(s)	Sirolimus gel placebo is administered topically twice a day for 12 weeks.
Outcome(s)	Primary Outcome(s): Improvements in angiofibroma [Time Frame: 12 weeks] Improvements comparing with baseline is assessed using photograph by the central photo-judgement committee See trial record for full list of other outcomes.
Results (efficacy)	Sixty-two patients (27 paediatric and 35 adults; 34 [55%] female; mean [SD] age, 22.5 [11.9] years) were enrolled and randomly assigned to receive sirolimus gel, 0.2% (30 patients), or placebo (32 patients). The response rates of angiofibromas at weeks 4, 8, and 12 of treatment were 0 each in the placebo group in contrast to 20% (95% CI, 8%-39%; P = .01), 43% (95% CI, 26%-63%; P < .001), and 60% (95% CI, 41%-77%; P < .001), respectively, in the sirolimus group.[11] Regarding the primary end point of composite improvements in angiofibroma at week 12, none of the 31 assessable patients in the placebo group were rated improved or better, and 26 of them (84%) were rated unchanged. In contrast, 5 (17%) and 13 (43%) patients in the sirolimus group were rated markedly improved and improved, respectively (P < .001).[11]

	In the sirolimus group, moreover, the response rates were significantly higher in paediatric patients (85%; 95% CI, 55%-98%) than in adult patients (41%; 95% CI, 18%-67%) (P = .03) at week 12 of treatment.[11]
Results (safety)	Adverse events were mild to moderate and were observed in 27 (90%) and 22 (69%) patients in the sirolimus and placebo groups, respectively; however, none of the trial participants discontinued treatment. Acute pancreatitis developed as a serious adverse event in 1 patient in the sirolimus group, and the patient recovered soon after hospitalization without discontinuing treatment.[11]

ESTIMATED COST

The cost of topical sirolimus is currently unknown.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

- Tuberous Sclerosis Association (TSA). UK guidelines for managing tuberous sclerosis complex. 2019.[22]

ADDITIONAL INFORMATION

Nobelpharma Co Ltd. 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.

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