Health Technology Briefing
September 2023

Topical rapamycin cream for treating facial angiofibroma

Company/Developer	Aft Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28727	NICE TSID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Topical rapamycin cream is in clinical development for the treatment of facial angiofibroma (FA) associated with tuberous sclerosis complex (TSC). TSC is a rare genetic disorder that affects genes that regulate cell growth. TSC is often associated with FA, which are pinkish or reddish bumps usually located on the cheeks, nose and chin. Although FAs are benign, they can bleed, block nasal passages, cause facial disfigurement, and impair patient functions such as vision and breathing. Typical treatments include laser surgery (using heat to destroy abnormal cells), cryotherapy (using extreme cold to freeze abnormal cells) and dermabrasion (mechanically wearing away abnormal cells). However, these treatments can be painful, may lead to scarring and do not prevent recurrence. Therefore, other less invasive treatment options are required.

Rapamycin is an immunosuppressant (a medicine that reduces the activity of the immune system) which inhibits a signalling pathway associated with cell growth, division and function. In patients with TSC, this pathway is dysregulated leading to the growth, survival and division of tumour cells. By blocking this pathway, rapamycin suppresses FA growth. Topical rapamycin is applied locally once a day and is therefore non-invasive. If licensed, topical rapamycin would offer an additional treatment option for patients with FA associated with TSC.

Proposed Indication

Treatment of facial angiofibroma (FA) associated with tuberous sclerosis complex (TSC) in patients aged 6 years and older.[1]

Technology

Description

Rapamycin (pascomer[2], TMB-002, sirolimus[1]) is a non-calcineurin inhibiting immunosuppressant.[3] It inhibits the mammalian target of rapamycin (mTOR) signalling pathway, which is often activated in tumours. The mTOR signalling pathway regulates gene transcription and protein synthesis to control cell proliferation and immune cell differentiation, and also plays an important role in tumour metabolism.[4] The mTOR signalling pathway is dysregulated by genetic disorders such as TSC.[5]

Topical rapamycin is currently in clinical development for the treatment of FA associated with TSC. In the phase II/III clinical trial (NCT03826628), rapamycin cream topical 0.5% or 1.0% w/w was applied on the affected area once daily in the evening for 26 weeks.[1]

Key Innovation

The current treatments for TSC-associated FA include laser surgery, cryotherapy and dermabrasion. These treatments can be painful, may lead to scarring and do not prevent recurrence of lesions[5]. In addition, since these invasive treatments are often difficult to administer to young children or patients with developmental disabilities, they are often not given to patients until the condition became serious.[6] Topical formulations of the mTOR inhibitor rapamycin have been reported to be effective and generally well tolerated for the management of FA based on several short-term studies, which was further established over the long term. The health-related quality of life in patients with FA has also significantly improved.[7]

If licensed, topical rapamycin will provide a new treatment option for patients with TSC-associated FA.

Regulatory & Development Status

Rapamycin cream is not licensed for any indication in the UK/EU.

Rapamycin cream is also in phase II/III clinical development for several indications, some of which are: [8]

- Vitiligo
- Solid Organ Transplant Recipients
- Skin Cancer

Patient Group

Disease Area and Clinical Need

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder caused by mutations in the *TSC1* or *TSC2* genes involved in regulating cell growth. TSC is characterised by hamartomas (benign lesions composed of aberrant disorganised growth of mature tissues) in various organs including the skin.[9,10] Around 75% of patients with TSC develop FA, which are multiple small, pinkish, erythematous hamartomas associated with spontaneous bleeding, pain, risk of infection, facial disfigurement and impairment of patient functions such as vision and breathing.[5,7] FAs usually appear by 5 years old 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.[9] In around 3 in 4 cases, the genetic fault occurs for no apparent reason in people without any other affected family

members. In the remaining 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.[11]

The incidence of TSC is estimated to be between 1/6000 and 1/10,000 live births and the population prevalence is estimated to be 1/20,000. Approximately 1 in 12,000–14,000 children under 10 years of age have TSC according to population-based studies in the UK. Globally, TSC is thought to affect 1 to 2 million individuals.[10] One UK study found the mortality rate in their cohort to be 5%.[10]

Recommended Treatment Options

There is no cure for TSC, and there are currently no licensed or NICE recommended pharmacological treatment options.[11] Other treatment options for TSC-associated FAs include:[5]

- laser surgery
- cryotherapy
- dermabrasion

Clinical Trial Information

Trial	NCT03826628, A Phase 2/3, Multi-Center, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Dose-Response Comparison of the Efficacy and Safety of a Topical Rapamycin Cream for the Treatment of Facial Angiofibromas (FA) Associated With Tuberous Sclerosis Complex (TSC) in Patients 6 Years of Age and Over **Phase II/III:** Completed **Location:** Four EU countries, USA and other countries **Primary completion date:** September 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N = 107 (actual); all sexes; aged 6 to 65 years; subjects diagnosed with TSC and presenting visible FAs
Intervention(s)	• 0.5% rapamycin cream applied topically once daily in the evening for 26 weeks • 1.0% rapamycin cream applied topically once daily in the evening for 26 weeks
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: Percentage of participants obtaining successful treatment (Time frame: 26 weeks) See trial record for full list of other outcomes.
Results (efficacy)	The clinical study demonstrated that both 1% and 0.5% rapamycin cream resulted in significant and clinically meaningful improvements across multiple efficacy assessments.[12] The percentage of subjects with a two-grade IGA (investigator's global assessment) improvement was greater in the 0.5% treatment group (11.1%) and 1% group (9.1%) than the placebo group (5.3%). However, this was not statistically significant (0.5%: OR 1.71, 95% CI 0.36-8.18, p = 0.499; 1%: OR 1.68, 95% CI 0.33-8.40, p = 0.530). Subjects with at least a one-grade IGA

	improvement were significantly different compared to placebo (0.5%: 55.6%, OR 4.73, 95% CI 1.59-14.10, p = 0.005; 1%: 60.6%, OR 5.14, 95% CI 1.70-15.57, p = 0.004; placebo: 23.7%).[12]
Results (safety)	Skin adverse reactions were more common in patients following rapamycin application (64%) compared to placebo (29%).[12]

Estimated Cost

The cost of topical rapamycin cream is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline in development. Sirolimus for treating angiofibroma from tuberous sclerosis complex in people 6 years and older (GID-TA10883). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Tuberous Sclerosis Association (TSA). UK guidelines for managing tuberous sclerosis complex. 2019.[13]

Additional Information

Aft Pharmaceuticals 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

1 Clinicaltrials.gov. *Dose-Ranging Efficacy and Safety Study of Topical Rapamycin Cream for Facial Angiofibroma Associated With Tuberous Sclerosis Complex*. 2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03826628 [Accessed 4 July 2023].

2 AFT Pharmaceutical. *AFT Completes Pascomer Clinical Study and Takes Back Rights in North America*. 2022. Available from: https://www.aftpharm.com/news/aft-completes-pascomer-clinical-study-and-takes-back-rights-in-north-america/ [Accessed 27 June 2023].

3 National Institute for Health and Care Excellence (NICE). *Sirolimus*. 2023. Available from: https://bnf.nice.org.uk/drugs/sirolimus/ [Accessed 4 July 2023].

4 Zou Z, Tao T, Li H, Zhu X. mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. *Cell & Bioscience*. 2020;10(1):31. Available from: https://doi.org/10.1186/s13578-020-00396-1.

5 Koenig MK, Bell CS, Hebert AA, Roberson J, Samuels JA, Slopis JM, et al. Efficacy and Safety of Topical Rapamycin in Patients With Facial Angiofibromas Secondary to Tuberous Sclerosis Complex: The TREATMENT Randomized Clinical Trial. *JAMA Dermatology*. 2018;154(7):773-80. Available from: https://doi.org/10.1001/jamadermatol.2018.0464.

6 Nobelpharma Co. Ltd. *Sakigake Designation & Orphan Drug Designation. Rapalimus GEL 0.2% (mTOR inhibitor), Treatment for Angiofibroma in Tuberous Sclerosis. Marketing Approval Granted.* 2018. Available from: https://www.nobelpharma.co.jp/_cms/wp-content/uploads/2020/07/20180326_en.pdf [Accessed 4 July 2023].

7 Boggarapu S, Roberds SL, Nakagawa J, Beresford E. Characterization and management of facial angiofibroma related to tuberous sclerosis complex in the United States: retrospective analysis of the natural history database. *Orphanet Journal of Rare Diseases*. 2022;17(1):355. Available from: https://doi.org/10.1186/s13023-022-02496-2.

8 Clinicaltrials.gov. *Rapamycin cream | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/results?cond=&term=Rapamycin+cream&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&phase=1&phase=2.

9 Wataya-Kaneda M, Nagai H, Ohno Y, Yokozeki H, Fujita Y, Niizeki H, et al. Safety and Efficacy of the Sirolimus Gel for TSC Patients With Facial Skin Lesions in a Long-Term, Open-Label, Extension, Uncontrolled Clinical Trial. *Dermatology and Therapy*. 2020;10(4):635-50. Available from: https://doi.org/10.1007/s13555-020-00387-7.

10 Kingswood C, Bolton P, Crawford P, Harland C, Johnson SR, Sampson JR, et al. The clinical profile of tuberous sclerosis complex (TSC) in the United Kingdom: A retrospective cohort study in the Clinical Practice Research Datalink (CPRD). *European Journal of Paediatric Neurology*. 2016;20(2):296-308. Available from: https://doi.org/10.1016/j.ejpn.2015.11.011.

11 National Health Service (NHS). *Overview: Tuberous sclerosis*. 2021. Available from: https://www.nhs.uk/conditions/tuberous-sclerosis/ [Accessed 4 July 2023].

12 Aitken P, Stanescu I, Boddington L, Mahon C, Fogarasi A, Liao Y-H, et al. A novel rapamycin cream formulation improves facial angiofibromas associated with tuberous sclerosis complex: a double-blinded, randomised, placebo-controlled trial. *British Journal of Dermatology*. 2023:ljad243. Available from: https://doi.org/10.1093/bjd/ljad243.

13 The Tuberous Sclerosis Association. *UK guidelines for managing tuberous sclerosis complex*. 2019. Available from: https://tuberous-sclerosis.org/wp-content/uploads/2019/10/SummaryofUKguidelinesformanagingTSCFINAL.pdf.

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.