Topical Sirolimus 0.2% Gel for Facial Angiofibroma Associated with Tuberous Sclerosis Complex in the United States: A Cost-Effectiveness Analysis

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BACKGROUND

- A rare autosomal dominant disorder that affects multiple organ systems, tuberous sclerosis complex (TSC) depicts diverse clinical manifestations associated with mutations in the *TSC1* or *TSC2* genes.[1] Facial angiofibromas, one of the predominant cutaneous manifestations of TSC, occurs in 83%-90% of TSC individuals.[2] Enlarged angiofibromas can bleed spontaneously, be painful and impair facial appearance, and hence impact the patient's quality of life, necessitating timely diagnosis and treatment.[3]
- The economic burden of facial angiofibroma associated with TSC and the cost-effectiveness of its treatments needs comprehensive evaluation. With the recent approval of the mechanistic target of rapamycin (mTOR) inhibitor, topical sirolimus 0.2% gel in the United States (US) for adults and children aged ≥ 6 years,[4] it remains of interest to determine whether introducing this drug in the US is a cost-effective strategy than other therapeutics (physical therapies, systemic therapies and combinations of both) for facial angiofibroma associated with TSC.
- A cost-effectiveness analysis was conducted using a semi-Markov model comparing topical sirolimus 0.2% gel to best supportive care (BSC) for managing facial angiofibroma associated with TSC from a US third-party (Commercial and Medicaid) perspective.

OUTCOMES OF INTEREST

- Incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALY) gained, costs of treatments (in the 2021 US dollar [USD]), and QALYs gained.

METHODS

PATIENT POPULATION

- Patients' characteristics and demographics were derived from a phase III, multicenter, randomized, placebo-controlled study by Wataya-Kaneda et al. 2018[5] and a long-term (52-week) study[6] of topical sirolimus 0.2% gel.
- The model considered children ≥ 6 years as described previously[5] and as suggested by the Food and Drug Administration.

MODEL STRUCTURE

- A 4-state transition semi-Markov model was used over a lifetime horizon to compare the cost-effectiveness of topical sirolimus 0.2% gel for facial angiofibroma associated with TSC versus BSC (procedures only, medication only, and procedure combined with medication) and mono/compounded therapies as per established standards.[7-9] Patients were only in one health state at a time.[10]
- The semi-Markov model schematic and structure are shown in **Figure 1**.

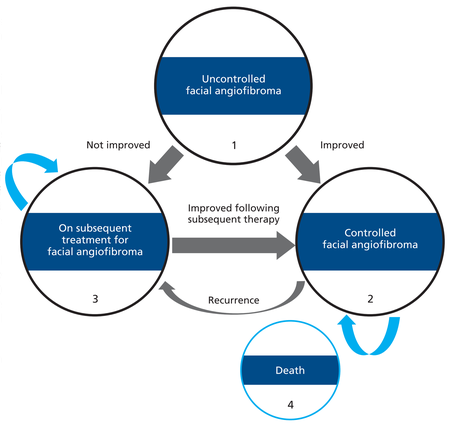
DATA SOURCE

The four health states included:

- **Uncontrolled facial angiofibroma:** intervention is administered for all patients with facial angiofibroma associated with TSC.
- **Controlled facial angiofibroma:** intervention is administered for patients with improvements (improved and markedly improved) in facial angiofibroma status, eventually transitioning to the controlled facial angiofibroma state and being in such a state until recurrence or until the patient goes off treatment. Patients who go off treatment will be in a tunnel state: "Controlled facial angiofibroma off-treatment." It is assumed that 100% of alive patients in the "Controlled facial angiofibroma off treatment" state will move to the "On subsequent treatment for facial angiofibroma" state at the end of the current cycle.
- **Subsequent treatment for facial angiofibroma:** if facial angiofibroma has not improved in patients (slightly improved, unchanged, slightly exacerbated, or exacerbated) after treatment for at least 12 weeks, or if patients come back to this health state from a state of 'controlled facial angiofibroma.'
- **Death:** captures all-cause mortality in the US or death related to TSC, whichever is higher.

- The model horizon in base case was considered as lifetime.
- Model inputs were obtained from phase III[5] and long-term study,[6] published pieces of literature, claims database analysis,[11] and US Government data and drug prices from real-world evidence (RWE) study.[12]

Figure 1. Model structure



Note: 1-4 are mutually exclusive and exhaustive health states. Transitions between various health states were determined based on disease improvement, recurrence, and subsequent treatment initiation

EFFICACY

- Investigator assessed composite improvement from baseline in size and redness of facial angiofibroma was used for efficacy inputs.[5] Our analysis derived the efficacy inputs from NPC-12G1[13] (first 12 weeks) and NPC-12G2 (beyond 12 weeks).[14]

HEALTH-RELATED QUALITY OF LIFE

- Regarding the health-related quality of life weights, the mean scores of short-form 36 (SF-36) dimensions[15] was converted into mean EuroQoL five-dimensional (EQ-5D) scores using the prescribed algorithm in the literature.[16]
- **Table 1** shows the distribution of the QoL weights used in the model.

Table 1. Distribution of QoL weights (mean) for different cohorts

Uncontrolled facial angiofibroma	Controlled facial angiofibroma		On subsequent treatment facial angiofibroma
	On treatment	Off treatment	
0.4828	0.5426	0.5426	0.4828

MORTALITY

- Mortality risk associated with TSC was considered from published literature.[17]
- The 2018 general age-specific all-cause mortality from the Centres for Disease Control and Prevention for the US general population and TSC-specific mortality rates were compared for each age group. The higher rate was applied in the model to estimate the mortality in each cycle.

COSTS

- The wholesale acquisition cost (WAC) of topical sirolimus 0.2% gel, derived based on WAC of 10 gm topical sirolimus tube, was assumed to be $1,750.[18] The assumed weekly drug acquisition cost was $735 for patients aged 6–11 years, $980 in those ≥ 12 years, and $932.58 (daily dose of 761 mg) in all patients.
- **Table 2** describe costs of different healthcare resource utilization from a sample of 4,446 patients with facial angiofibroma.

Table 2. Healthcare resource utilization costs in patients with facial angiofibroma

Parameters	Best Supportive Care	Procedure + medication	Procedure only	Medication only	Sirolimus
Inpatient hospitalization	$20,695	$20,695	$20,695	$20,695	$20,695
Emergency visits	$2,280	$2,280	$2,280	$2,280	$2,280
Office visits	$3,114	$3,114	$3,114	$3,114	$3,114
Other outpatient visits[1]	$44,443	$44,443	$44,443	$44,443	$44,443
Outpatient pharmacy[2]	$57,649	$31,947	$12,621	$62,986	$16,259
Total costs	$128,181	$102,479	$83,153	$133,518	$86,791
Weekly costs	$2,457	$1,964	$1,594	$2,559	$1,663

1. Outpatient visits that are non-emergency department and non-office.
2. No facial angiofibroma-related pharmacy cost for best supportive care is assumed; hence pharmacy costs from without facial angiofibroma is used as a proxy.

- The costs for different healthcare resource utilization are assumed to be same for patients with facial angiofibroma except the outpatient pharmacy costs.
- Due to limited number of patients in procedure only and procedure combined with medication, the costs figure was highly uncertain. Hence, equal costs for all healthcare resource utilization except outpatient pharmacy was assumed.

SENSITIVITY ANALYSES

- The willingness-to-pay (WTP) thresholds for the ICERs were set at a range of $50,000 to $150,000 as per the Institute of Clinical Evidence and Review's Value Assessment Framework.[19]
- Probabilistic sensitivity analysis (PSA) assumed suitable probability distributions for distinct parameters. QALY and cost differences between topical sirolimus 0.2% gel and BSC were analyzed using 1,000 iterations in the base-case settings and probability distributions in a cost-effectiveness scatterplot.

RESULTS

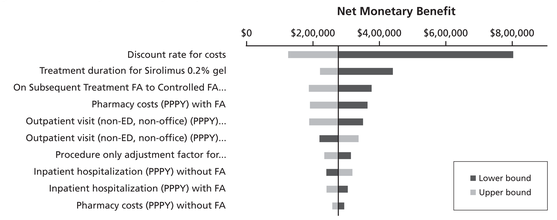
BASE-CASE ANALYSES

- The incremental cost for topical sirolimus 0.2% gel is -$246,230 with an incremental QALY gain of 0.28, suggesting the treatment is more effective and less costly against BSC for treatment of facial angiofibroma associated with TSC in the US.
- A net monetary benefit of $273,890 per patient is estimated if patients are treated with topical sirolimus 0.2% gel at $100,000 WTP/QALY gained.

ONE-WAY SENSITIVITY ANALYSIS

- The cost-effectiveness of topical sirolimus 0.2% gel had an exceedingly high level of uncertainty. ICER remained above the $100,000/QALY WT Pthreshold for top 10 impacting parameters **(Figure 2).** The model is most sensitive to the discount rate for costs, sirolimus 0.2% gel treatment duration and the transition rate from subsequent treatment to controlled facial angiofibroma (on treatment) among all parameters.

Figure 2. Tornado diagram for one-way sensitivity analysis

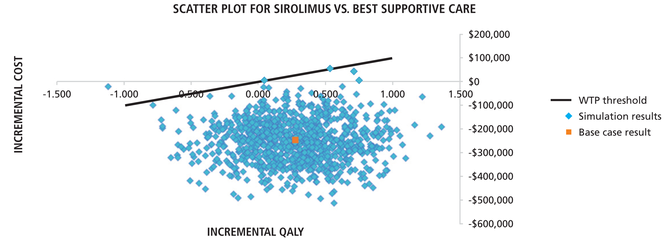


ED, emergency department; FA, facial angiofibroma; PPPY, per patient per year

PROBABILISTIC SENSITIVITY ANALYSIS

- Scatter plot of all 1,000 Monte-Carlo simulations (**Figure 3**) showed maximum number of points lie in the south-eastern quadrant which signifies that sirolimus 0.2% gel is more effective but less costly and also establish the robustness of the model around the base case results. Topical sirolimus 0.2% gel was > 99% likely to be cost-effective at a WTP threshold of $50,000 per QALY.

Figure 3. Probabilistic sensitivity analysis



WTP, willingness-to-pay; QALY, quality adjusted life years

CONCLUSIONS

- The semi-Markov model used in our study for identifying the cost-effectiveness of facial angiofibroma associated with TSC suggests that topical sirolimus 0.2% gel is a cost-effective treatment option compared with BSC in the US. These findings will help inform decision makers such as payers and healthcare providers in the US.
- Value-based pricing analysis showed that WAC for topical sirolimus 0.2% gel was under-priced by ~47% at a WTP threshold of $50,000 per QALY gained ($2,581), ~50% at a WTP $100,000 per QALY gained ($2,626), and ~53% at a WTP $150,000 per QALY gained ($2,670).
- Our extensive sensitivity and scenario analysis supported the base-case results, attesting to their robustness across various changes in parameter estimates and alternate modeling assumptions.

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