NCPE Assessment

Technical Summary

Anifrolumab (Saphnelo®)

HTA ID: 23027

30 July 2025

Applicant: Astra Zeneca

Anifrolumab, as an add-on therapy, for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus, despite standard therapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of anifrolumab (Saphnelo®).

Following assessment of the Applicant's submission, the NCPE recommends that anifrolumab (Saphnelo®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Astra Zeneca) Health Technology Assessment of anifrolumab (Saphnelo®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In May 2024, Astra Zeneca submitted a dossier which investigated the clinical effectiveness and safety, cost-effectiveness and budget impact of anifrolumab (Saphnelo®) as an add-on therapy for the treatment of adult patients with moderate to severe, active auto antibody-positive systemic lupus erythematosus (SLE), despite standard therapy. Astra Zeneca are seeking reimbursement in the hospital setting.

SLE is a heterogenous, chronic autoimmune disease with multisystem involvement. Clinical manifestations can range from mild self-resolving symptoms to severe life-threatening organ involvement. The mucocutaneous and musculoskeletal systems are most commonly affected. SLE can also affect the renal, cardiovascular, neuropsychiatric, or pulmonary systems. SLE disproportionally affects women of childbearing age. Patients are often prone to relapses and remissions. Several tools and indices are available to assess disease activity, including the SLE Disease Activity Index 2K (SLEDAI-2K), the British Isles Lupus Assessment Group 2004 (BILAG-2004) Index, and the Physician Global Assessment (PGA). In clinical practice, disease activity is assessed using certain components of the SLEDAI-2K and/or other outcomes such as the ability to taper steroid dosage as well as assessments of clinical manifestations.

Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). Anifrolumab inhibits the binding of type I interferon to IFNAR1 blocking the biologic activity of type I interferons. The recommended dose of anifrolumab is 300mg, administered as an intravenous infusion over a 30-minute period, once every four weeks. Anifrolumab is, potentially, a long-term treatment. The product licence does not make a recommendation on treatment duration nor does it recommend a timepoint for assessment of response.

Anifrolumab is an add-on therapy to standard of care (SOC). SOC is a basket of treatments containing hydroxychloroquine, an immunosuppressant (methotrexate, azathioprine, or mycophenolate mofetil) and oral corticosteroids. The relevant comparator is SOC alone.

1. Comparative effectiveness of anifrolumab

The clinical trial programme included two phase III, double-blind, randomised, placebo-controlled trials (RCTs) – TULIP 1 and TULIP 2 followed by a three-year double-blind placebo-controlled long-term extension study (TULIP-LTE).

Both RCTs had similar trial design, consisting of a four-week screening period and a 52-week, double-blind treatment period. In addition to SOC treatment, participants were randomised in a 2:1:2 ratio to receive either placebo, anifrolumab 150mg, or anifrolumab 300mg, once every four weeks (TULIP 1) or in a 1:1 ratio to receive either placebo or anifrolumab 300mg, once every four weeks (TULIP 2). The anifrolumab 150mg dosage regimen is not licensed and is not discussed further here. In both RCTs, an oral-corticosteroid tapering attempt was mandated between week 8 and week 40 among participants taking at least 10mg per day oral prednisone or equivalent at baseline. The target dose following tapering was 7.5mg or less per day.

The primary endpoints were response at week 52 evaluated using either the SLE Responder Index (SRI(4)) (TULIP 1) or the British Isles Lupus Assessment Group-based Combined Lupus Assessment (BICLA) (TULIP 2). In addition, two intercurrent events (discontinuation of study treatment and use of restricted medications beyond the protocol-allowed thresholds) were classified as non-responses in the composite primary endpoints. Participants who withdrew from the RCTs were also categorised as non-responders.

Baseline characteristics were generally similar across both RCTs and were well-balanced between treatment arms. Overall, 72% of participants had high disease activity (SLEDAI-2K score ≥ 10). The most commonly affected organ systems were the mucocutaneous (TULIP 1: 87%, TULIP 2: 85%) and musculoskeletal (TULIP 1: 89%, TULIP 2: 88%) systems. Most participants were taking oral corticosteroids at baseline (80%), with approximately half of participants taking at least 10mg per day. In TULIP 1 and TULIP 2 respectively, 20% and 15% of participants receiving anifrolumab, and 21% and 29% of participants receiving placebo discontinued treatment prior to week 52. The Review Group note the marked imbalance in treatment discontinuations in TULIP 2.

The primary endpoint of TULIP 1 was not met with 49% (88 of 180) and 43% (79 of 180) of participants meeting the SRI(4) response criteria at week 52 in the anifrolumab + SOC arm and placebo + SOC arm, respectively (difference: 6.0%; 95% confidence interval (CI) -4.2 to 16.2). However, BICLA response (secondary endpoint) at week 52 was improved in the anifrolumab + SOC arm compared with the placebo + SOC arm (47.1% versus 30.2%; difference: 17.0%; 95% CI 7.2 to 26.8). The primary endpoint of TULIP 2 was changed to BICLA following failure of the TULIP 1 on its primary endpoint. This change was made while TULIP 2 trial was still blinded. At week 52, 47.8% (86 of 180) and 31.5% (57 of 182) of participants met the BICLA response criteria (difference: 16.3%; 95% CI 6.3 to 26.3; p=0.001). In the European Public Assessment Report, it is acknowledged that the failure of TULIP 1 on its primary endpoint remains a notable weakness of the clinical development programme. However, following consultation with an ad-hoc expert group, the Committee for Human Medicinal Products concluded that the totality of the evidence was supportive of a beneficial treatment effect of anifrolumab. In particular, the treatment difference in BICLA response in both studies was considered to be clinically meaningful.

The Review Group consider that treatment benefit of anifrolumab, as measured by the primary endpoints, is likely to be overestimated due to the classification of intercurrent events (discontinuation of study treatment and use of restricted medication) as non-responses. Results from a sensitivity analysis based on modified endpoints using the three clinical disease activity components only (i.e., a treatment policy estimand) show a reduced treatment benefit. Furthermore, in TULIP 2, the difference in proportion of BICLA non-responders across the two treatment arms was mainly driven by the imbalance in study withdrawals, with 10% and 20% of participants withdrawing (and hence categorised as non-responders) from the anifrolumab + SOC arm and placebo + SOC arm, respectively. When only clinical criteria were considered for assessment of BICLA response, outcomes were similar between arms.

The Applicant presented results from a post-hoc analysis of pooled data from the TULIP RCTs on Lupus Low Disease Activity State (LLDAS) attainment. The LLDAS criteria include control of disease activity (based on SLEDAI-2K and the PGA instruments) combined with requirements on the use of immunosuppressive medications (including a prednisone or equivalent dose of

≤ 7.5mg per day). In the TULIP RCTs, patients who discontinued treatment due to lack of efficacy and/or disease worsening were also automatically categorised as LLDAS non-responders. At week 52, more participants attained LLDAS with anifrolumab + SOC compared with placebo + SOC (30.0% (108 of 360) versus 19.7% (72 of 366), odds ratio 1.8; 95% CI 1.3 to 2.5; p=0.0011).

In relation to patient-reported outcomes, results from a post-hoc analysis of the pooled data from the TULIP RCTs, showed that BICLA responders had greater mean improvements from baseline at week 52 in Patient Global Assessment, Short Form (SF)-36, Lupus Quality of Life, FACIT-F, (Functional Assessment of Chronic Illness Therapy – Fatigue) and pain Numerical Rating Scale scores compared with BICLA non-responders. A greater proportion of BICLA responders also reported improvements greater than or equal to the minimum clinically important difference across all SF-36 domains, Lupus Quality of Life domains and FACIT-F.

2. Safety of anifrolumab

As per the Summary of Product Characteristics, the most commonly reported adverse reactions during treatment with anifrolumab were upper respiratory tract infection (34%), bronchitis (11%), infusion-related reaction (9.4%) and herpes zoster (6.1%). The most common serious adverse reaction was herpes zoster (0.4%). Serious hypersensitivity reactions including anaphylaxis have been reported following administration of anifrolumab. The incidence of hypersensitivity reactions was 2.8% in the anifrolumab group and 0.6% in the placebo group. The incidence of infusion-related reactions was 9.4% in the anifrolumab group and 7.1% in the placebo group. Infusion-related reactions were mild or moderate in intensity, none were serious, and none led to discontinuation of anifrolumab.

3. Cost effectiveness of anifrolumab

Methods

The Applicant submitted a cohort state-transition, cost-effectiveness model (CEM) comprising 12 health states based on a combination of LLDAS status (LLDAS or Not LLDAS) and organ damage measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (hereon SDI score). All

patients enter the model in the Not LLDAS health state (i.e., patients who have a SLEDAI-2K score that is greater than 4, have new disease activity, PGA score that is greater than 1, or use prednisone (or equivalent) at a dose greater than 7.5mg/day). Following the first six-month cycle, patients in the anifrolumab + SOC arm are classified as either Responders or Non-Responders depending on whether or not they transition to the LLDAS health states. The CEM incorporates a 6-month stopping rule where Non-Responders discontinue anifrolumab. Transitions between LLDAS and Not LLDAS can occur during subsequent cycles. Responders who lose response (i.e., transition to Not LLDAS) also discontinue anifrolumab. Once organ damage occurs, it is assumed to be permanent, and patients cannot transition to a lower SDI score. Transition to Death is possible from all health states.

The LLDAS health states are associated with lower mortality, reduced risk of organ damage, fewer SLE flares, and improved health-related quality of life. Consequently, the model depends on the validity of LLDAS as a surrogate for these outcomes. Although there is evidence that patients achieving LLDAS have more favourable SLE outcomes (individual-level surrogacy), it has not been established that improvements in LLDAS attainment rates with treatment will lead to improvements in SLE outcomes (i.e., there is no evidence of trial-level surrogacy). The use of LLDAS attainment to model clinical response and determine treatment stopping rules in the model is not aligned with the product licence nor Irish clinical practice, where less stringent response criteria are used to inform treatment decisions.

Transitions between LLDAS and Not LLDAS health states were informed by individual patient data from the TULIP RCTs and LTE. Missing and post-discontinuation LLDAS observations (which were categorised as non-response) occurred to a greater extent in the SOC alone arm which may bias the cost-effectiveness results in favour of anifrolumab. Furthermore, the high rates of non-continuation into TULIP-LTE, leads to small sample sizes and possible selection bias affecting the estimation of long-term transition probabilities. Other key treatment effectiveness parameters which determine mortality, flare rates and risk of organ damage, were obtained from published observational studies. These studies appear not to have been identified in a systematic manner. It is possible that alternative sources exist, the use of which may change the cost-effectiveness results. Treatment-independent utility values for the LLDAS and Not LLDAS health states were derived from EQ-5D data collected in

the TULIP RCTs. Disutilities associated with adverse events, organ damage, flares and higher oral corticosteroid usage in the Not LLDAS health states were also included in the CEM.

Certain Review Group concerns were addressed in the NCPE adjusted base case:

- Key input parameters, used to model the impact of LLDAS attainment on SLE outcomes, were estimated using proxy measures (either spending at least 50% of time in LLDAS or attaining LLDAS at least once) which may not reliably measure the impact of current LLDAS status on these outcomes. In particular, the effect of LLDAS on mortality was likely overestimated by this approach, and an alternative source was used, for this parameter, in the NCPE adjusted base case.
- Use of utilities derived from the anifrolumab + SOC arm to inform the LLDAS and Not LLDAS health state utilities in both treatment arms are likely to introduce bias. In the NCPE adjusted base case, LLDAS and Not LLDAS health state utilities were estimated using pooled data from both treatment arms of the TULIP RCTs.
- Inclusion of disutilities for flares and higher oral corticosteroid usage in the Not LLDAS health states leads to double couniting as these are already accounted for in the health state utility values. These disutilities were not included in the NCPE adjusted base case.
- The use of different approaches to estimate direct medical resource use costs in the LLDAS and Not LLDAS health state introduces bias in favour of anifrolumab. In the NCPE adjusted base case these costs were informed by a single literature source.

The NCPE adjusted base case changes does not address the uncertainties arising from the use of LLDAS to predict clinical outcomes and to inform treatment stopping rules. It is likely that a lower proportion of patients (than predicted in the CEM) will discontinue anifrolumab, in clinical practice, due to the use of less stringent response criteria. Thus, the treatment costs of anifrolumab are likely to be underestimated in this submission.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE adjusted base cases are shown in Table 1 and Table 2, respectively.

Table 1: Applicant base case incremental cost-effectiveness results[b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SOC alone	212,921	8.479	-	-	-
Anifrolumab + SOC	226,547	8.604	13,626	0.125	109,218

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **SOC:** standard of care.
[a] Corresponding probabilistic ICER using 1,000 iterations =€106,829/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SOC alone	171,712	9.421	-	-	-
Anifrolumab + SOC	187,838	9.504	16,126	0.083	194,988

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care
[a] Corresponding probabilistic ICER using 1,000 iterations =€188,870/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes

Sensitivity analysis

Under the NCPE adjusted base case the probabilities of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 0% at both thresholds. Under the Applicant base case the probability of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 0% and 1.4% respectively.

Under the NCPE adjusted base case, a discount of 99.6% and 86.7% would be required for anifrolumab + SOC to be considered cost-effective at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY, respectively.

4. Budget impact of anifrolumab

The price to wholesaler for a single anifrolumab 300mg vial is €1,020. Applying a Framework Agreement rebate of 9%, the cost of treating a patient for one year with anifrolumab alone is €15,168 including VAT.

Based on a Market share estimate of 10% in Year 1, increasing to 50% in Year 5, and applying the 6-month stopping rule, the Applicant estimates the five-year cumulative gross drug-budget impact for anifrolumab (excluding SOC costs) to be €4.66 million including VAT. The Review Group note the considerable uncertainty associated with the market share estimates and stopping rule assumptions. When the stopping rule assumption is removed and

discontinuations each year are set in-line with the TULIP RCTs the five-year cumulative gross drug-budget impact is an estimated €10 million including VAT.

5. Patient Organisation Submission

A patient organisation submission was received from Arthritis Ireland.

6. Conclusion

The NCPE recommends that anifrolumab (Saphnelo®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

** This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013*