Report Saphnelo® - anifrolumab

Product & Mechanism of action

Substance: anifrolumab

Brand Name: Saphnelo

Originator/licensee: AstraZeneca AB

Classification:NCE

ATC code:L04AA51

OrphanStatus:
Eu: No
Us: No

Mechanism of action:
Anifrolumab is a mAbthat binds to subunit 1 of the type I IFNAR. This binding inhibits type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalization of IFNAR1, thereby reducing the levels of cell surfaceIFNAR1 available for receptor assembly. Blockade of receptor-mediated type I IFN signaling inhibits IFN responsivegene expression and downstream inflammatory and immunological processes[1].

Authorized indications Licensing status

Authorized Indication:
EMA:anifrolumabis indicated as an add-on therapy for the treatment of adult pts with moderate to severe, active autoantibody-positive SLE, despite standard therapy [2].

FDA: anifrolumab is indicated for the treatment of adult pts with moderate to severe SLE, who are receiving standard therapy[1].

Route of administration:IV

Licensing status
EU CHMP P.O. date: 16/12/2021
FDA M.A. date: 30/07/2021

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: No

ABBREVIATIONS:
AE: adverse event
BICLA: BILAG-based Composite Lupus Assessment
BILAG: British Isles Lupus Assessment Group
CHMP: Committee for Medicinal Products for Human Use
IFN: interferon
IFNAR: interferon-alpha receptor 1
M.A.: Marketing Authorization
mAb: monoclonal antibody
PGA: Physician's Global Assessment
P.O.: Positive Opinion
Pts: patients
SLE: systemic lupus erythematosus
SLEDAI-2K: SLE Disease Activity Index 2000
SRI(4): SLE Responder Index

Essential therapeutic features

Summary of clinical EFFICACY:
The efficacy of anifrolumab was evaluated in three 52-week, randomized, double-blind, placebo-controlled trials: the phase 2 "MUSE" trial (**NCT01438489**) [3], the phase 3 "TULIP-1" (**NCT02446912**)[4] and the"TULIP-2" (**NCT02446899**)[5] trials.Ptswere aged ≥18 years and had moderate to severe activeSLE, with a SLEDAI-2K score ≥6, organs involvement based on BILAG assessment, and a PGA score ≥1. All pts. were also required to be receiving a stable, standard SLE therapy (e.g. oral corticosteroids, antimalarials and/or immunosuppressants) and continued their therapy during the trial, with the exception of biologics and protocol-prohibited immunosuppressants (such as cyclophosphamide and IFN therapy). Ptswere randomized to receive placebo orIV anifrolumabevery four weeks. Number of enrolled pts, allocations and primary endpoints of the three trials are summarized in the table below[3-5].

	NCT01438489	NCT02446912	NCT02446899
Number of enrolled pts and allocation	placebo: N=102 anifrolumab 300mg: N=99 anifrolumab 1,000mg: N=104	placebo: N=184 anifrolumab 150mg: N=93 anifrolumab 300mg: N=180	placebo: N=182 anifrolumab 300mg: N=180
Primary efficacy endpoints definition	Proportion of pts who achieved a SRI(4)[a] response at week 24, with a sustained reduction in oral corticosteroids from week 12 through week 24	Proportion of pts who achieved a SRI(4) response at week 52 in the anifrolumab 300mg group vsplacebo	Proportion of pts who had a BICLA[b] response at week 52
Efficacy results	The primary endpoint was met by 34.3% pts treated with anifrolumab 300mg (p=0.014) and 28.8% pts in the anifrolumab 1,000mg group (p=0.063) vs placebo (17.6%)	The primary endpoint was not met since the proportions of pts who achieved SRI-4 response were similar for anifrolumab 300mg (36%) and placebo (40%) (p=0.41)	A BICLA response occurred in 47.8% pts receiving anifrolumab vs 31.5% pts in placebo group (p=0.001)

The primary efficacy endpoint was not reached in the "TULIP-1" trial (**NCT02446912**), but severalsecondary endpoints, includingBICLA response, suggested thepossibility of clinical benefit of anifrolumab, although thestatistical significance was not formallyassessed [4].
In the "TULIP-2" trial (**NCT02446899**), the primary endpoint waschanged from SRI(4)to BICLA response, the last reaching a significative difference vs placebo [5].Given the clinical heterogeneity of SLE and the need to bring drugs to pts with SLE, the lupus community has urged regulatorsto consider trial designs allowing greaterflexibility in defining success [6].

Summary of clinical SAFETY:
The main safety results from NCT01438489, NCT02446912 and NCT02446899 trials are summarized in the table below [3-5].

	NCT01438489			NCT02446912			NCT02446899	
	placebo	anifrolumab 300mg	anifrolumab 1,000mg	placebo	anifrolumab 150mg	anifrolumab 300mg	placebo	anifrolumab 300mg
Any AEs	77.2%	84.8%	85.7%	78%	85%	89%	84.1%	88.3%
Serious AEs	18.8%	16.2%	17.1%	16%	11%	14%	17.0%	8.3%
Death	0	0	1	0	0	1	0	1
AEs leading to discontinuation	7.9%	3.0%	9.5%	3%	5%	6%	7.1%	2.8%

Ongoing studies:
- ***For the same indication:****Yes*
- ***For other indications:****No*

Discontinued studies (for the same indication): No

[a]**SRI(4)** is defined as a ≥4-point reduction in SLEDAI-2K score, no new BILAG-2004 A (severe) or <2new BILAG B (moderately severe) scores and <0.3-point deterioration in PGA.
[b]**BICLA** is defined as all of the following: a reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline to lower levels (BILAG-2004 B, C, or D and C or D, respectively) and no worsening in other organ systems (with worsening defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items); no worsening in disease activity (as determined by SLEDAI-2K score and by PGA score); no discontinuation of the trial intervention and no use of restricted medications beyond protocol-allowed thresholds.

References:
1.https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761123s000lbl.pdf
2.https://www-ema-europa-eu.translate.goog/en/medicines/human/summaries-opinion/saphnelo?_x_tr_sl=en&_x_tr_tl=it&_x_tr_hl=it&_x_tr_pto=op,sc
3.https://pubmed.ncbi.nlm.nih.gov/28130918/
4.https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(19)30076-1/fulltext
5.https://pubmed.ncbi.nlm.nih.gov/31851795/
6.https://www.nejm.org/doi/full/10.1056/NEJMe1915490
7.https://www.drugs.com/price-guide/saphnelo
8.https://pubmed.ncbi.nlm.nih.gov/26089119/
9.https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=IT&Expert=536
10.https://pubmed.ncbi.nlm.nih.gov/30926722/
11.https://clinicaltrials.gov/

NHS impact

Cost of therapy:
In the USthe cost for a supply of SaphneloIV solution (300mg/2mL, i.e. corresponding to afour-weektherapy) is around $4,812 [7].

Epidemiology:
An Italian study conducted in Brescia province found a prevalence of SLE of 39/100,000 (adults: 42/100,000; pediatricpopulation: 15/100,000) [8]. These figures are in line with the prevalence reported by Orphanet (1-5/10,000) [9].Theoverall annual incidence rate was found to be 2/100,000 [8].

POSSIBLE PLACE IN THERAPY:
Hydroxychloroquine represents the 1st-linetherapy in all SLE pts. Glucocorticoidscan be administered to provide rapid symptom relief, but their use during chronic maintenance treatment should be minimized. Initiation of immunomodulatoryagents (methotrexate, azathioprine, mycophenolate)can expedite the tapering/discontinuation of glucocorticoids andprevent flares. Cyclophosphamidecan be considered in organ-threatening disease and only as rescuetherapy in refractory non-major organ manifestations. Inpersistently active or flaring extra-renal disease with inadequate control to 1st-line treatments, add-on belimumab should be considered. Rituximab maybe considered in organ-threatening, refractory disease, but it is currently used off-label.[10]

OTHER INDICATIONS IN DEVELOPMENT: No

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:litifilimab, dapirolizumabpegol, obinutuzumab, baricitinib, forigerimod. [11]

*Service reorganization: No
*Possible off label use: No

Issued on: January 2022