Background Reported here is the characterization of cenerimo,
doxod, a novel, potent, selective, and orally active sphingosine-
1-phosphate receptor 1 (S1P1) modulator in the context of
SLE.
Methods Lymphocytes from patients with SLE and healthy
subjects were assessed for cenerimod-induced S1P1 receptor
internalization. Efficacy of cenerimod was evaluated in the
MRL/lpr lupus mouse model. In a 12-week phase 2 clinical
trial in SLE subjects treated with multiple doses of cenerimod
(NCT02472795), lymphocyte subsets and inflammatory bio-
markers were characterized.
Results Cenerimod was potent and efficacious at inducing
S1P1 receptor internalization in T and B lymphocytes with an
EC50 of ~15 nM in both healthy subjects and patients with
SLE. In lupus-like MRL/lpr mice treated with cenerimod, cir-
culating T and B lymphocytes were reduced, which resulted
in reduced immune infiltrates into tissue, reduced autoanti-
body production and inflammation, preserved organ function,
and increased survival. In SLE subjects treated with ceneri-
mod for 12 weeks, a dose-dependent reduction of circulating
T cells (95%), B cells (90%), and antibody-secreting cells
(85%) was evident. Furthermore, a reduction in anti-dsDNA
antibodies and IFN-α, two key inflammatory molecules, was
observed.
Conclusion Cenerimod was potent and efficacious in reduc-
ing S1P1 receptor surface expression on lymphocytes, result-
ning in reduced circulating T and B lymphocyte populations,
including antibody-secreting cells, and a decrease in inflam-
matory biomarkers in SLE subjects. Furthermore, cenerimod
significantly ameliorated systemic and organ-specific autoim-
munity in a mouse model of SLE. These results warranted
the further investigation of the clinical efficacy and safety of
cenerimod in the ongoing phase 2b clinical trial (NCT03742037).
Acknowledgements This research was funded by Idorsia Phar-
maceuticals Ltd.

Background SLE is an autoimmune disease characterized by
activation of the innate and adaptive arms of the immune
system. Recently the nuclear export protein exportin-1
(XPO1) has surfaced as an attractive target for the treatment
of SLE. Verdinexor is a potent, orally available and well-tol-
erated XPO1 inhibitor. Verdinexor inhibits the nuclear export
of ~220 cargoes, and this pleiotropic effect leads to dampen-
ing of the NF-κB and IL-6 responses and is linked to its
global anti-inflammatory effects. Thus, we examined the abil-
ity of verdinexor to alleviate the pathogenic mechanisms
underlying SLE.

Methods The minimal efficacious dose of verdinexor was
determined in mice with established disease. Mice were
dosed with verdinexor for four weeks, followed by treatment
cessation for four weeks. Then, escalating doses of verdi-
nexor were tested for their ability to control recurrent dis-
ease. We enumerated pathogenic plasma cells (PC),
plasmablasts (PB), and T cells in the spleen and bone marrow
(BM) and measured systemic inflammatory cytokines and che-
mokines. Elucidation of the mechanism of PC and PB deple-
tion in human BM from healthy and SLE patients is
underway.

Results Verdinexor treatment at 7.5 mg/kg weekly significantly
decreased germinal center B cells, PC and PB in the BM and
the spleen four weeks after resumption of treatment without
affecting normal cells. Furthermore, levels of pro-inflammatory
cytokines, chemokines, and B cell survival factors were all sig-
ificantly decreased. Results from assays in human BM have
confirmed these findings.

Conclusions Verdinexor has demonstrated efficacy in a murine
model of SLE by reducing generation, survival and function
of auto-reactive immune cells without affecting normal cells.
It is likely that inhibition of the NF-κB pathway and impaired
IL-6 production underlie verdinexor’s efficacy. Taken together
with our findings in human BM cells, these data suggest the
potential of verdinexor to have a significant impact on disease
progression in lupus patients.

Acknowledgements NIH Grant R44AI124949-03

Background Systemic lupus erythematosus (SLE) is a systemic
autoimmune disease, often presenting with neuropsychiatric
manifestations. Reports on the frequency and patterns of these
manifestations vary substantially and remain incompletely
understood. We examined neuropsychiatric manifestations in
the prospective nationwide cohort of Swiss SLE (SSCS)
patients and conducted a systematic literature review to re-
textualise our findings.

Methods We reviewed all patients included in the SSCS from
2007–2019 and classified severe neuropsychiatric manifesta-
tions. Searches were performed in relevant electronic databases
from 1.1999–1.2020 and by checking reference lists of the
pertinent literature. Authors of important papers were con-
tacted to obtain further (unpublished) studies. We included