

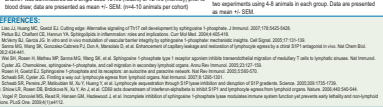
INTRODUCTION

Sphingosine 1-phosphate (S1P) is a biologically abundant lipid mediator that plays an essential role in cell signaling pathways, particularly in the immune system where changes in local S1P concentration and gradient can alter inflammatory cell responses.^{1,2} Inhibition of endothelial cells^{3,4} and modify lymphocyte migration patterns.^{5,6} The concentration gradient of S1P between lymphoid tissues and the peripheral blood is tightly regulated by both metabolic and catabolic enzymes. Sphingosine 1-phosphate lyase 1 (S1PL or S1PL1) is the main enzyme responsible for the degradation of S1P (Figure 1). Mice with reduced S1PL activity have significantly reduced circulating lymphocytes as a consequence of increased S1P content in lymphoid tissues.⁷

LX2931, also known as LX3305, is an orally-bioavailable small molecule inhibitor of S1PL, Figure 1 being developed by Lexicon Pharmaceuticals, Inc. as a potential therapeutic compound for the treatment of autoimmune and inflammatory disorders, such as rheumatoid arthritis (RA). In preclinical studies, LX2931 demonstrated potent anti-inflammatory activity in rodent models of arthritis, inflammation and transplantation. In Phase 1 studies, LX2931 was well tolerated at all dose levels tested and produced a dose-dependent reduction in circulating lymphocytes. In the current study, discussed here, co-administration of MTX with LX2931 was well tolerated over 14 days of dosing in patients with stable rheumatoid arthritis (RA). These results further support that inhibition of S1PL, with a small molecule therapy, such as LX2931, may represent a new mechanism for immune modulation with the potential to address inflammatory diseases such as RA as well as other autoimmune and inflammatory disorders.

PRELIMINARY RESULTS

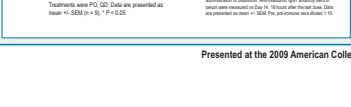
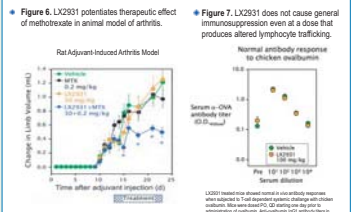
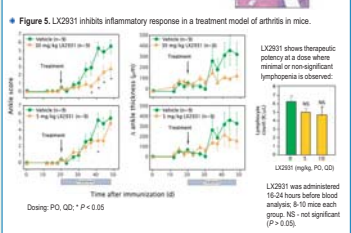
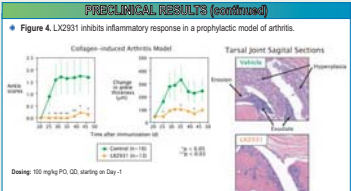
- A novel drug target (S1PL) was discovered through Lexicon's high-throughput mouse knockout program (Genome 2007⁸).
- Genetic inhibition of S1PL through the use of knockout mouse technology demonstrates significant reduction in circulating lymphocytes.⁷
- LX2931 recapitulates the lymphopenic phenotype observed in knockout mice in a dose-dependent manner in rodents and primates (Figure 2).
- Physiologic response to LX2931 treatment reveals a high tissue specificity as demonstrated by significant increases of S1P in the thymus, spleen, and jejunum compared to other tissues (Figure 3).
- LX2931 treatment delays alveolar rejection and ameliorates the development of inflammation in multiple animal models of disease, including rodent models of rheumatoid arthritis (Figure 4).
- LX2931 shows therapeutic potency at doses where lymphopenia is not observed (Figure 5).
- LX2931 potentiates the therapeutic effect of methotrexate (MTX) in a rat adjuvant arthritis model (Figure 6).
- Anti-inflammatory effects of LX2931 are not due to a generalized immunosuppression (Figure 7).
- Figure 2. LX2931 mechanism of action is conserved from mice to primates.
- Figure 3. LX2931 elevates S1P levels primarily in the lymphoid system.



LX2931 was administered as a single dose 10 mg (red) or 30 mg (blue) prior to blood draws. Data are presented as mean ± SEM. n=6-10 animals per group. Data are presented as mean ± SEM.

REFERENCES

1. Hata A, et al. Sphingosine 1-phosphate signaling: 1717
2. Hata A, et al. Sphingosine 1-phosphate signaling: 1717
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PHASE 1 STUDY RESULTS

- Two single-dose and two multiple-dose, placebo-controlled trials have been completed in healthy volunteers.
- Liquid and solid oral dose formulations behave similarly.
- Dose ranges tested from 10 mg to 250 mg.
- 108 active treatment participants; 36 placebo participants.
- Pharmacokinetic analyses support a once-daily dosing regimen, with steady-state levels achieved by Day 4 of dosing.
- Dose-dependent reduction in absolute lymphocyte counts (ALC) consistently observed throughout all studies, confirming preclinical results (Figure 8).
- Rapid onset and offset of pharmacologic activity: rises in ALC, as well as T- and B-cell subpopulations, observed 24 hours after single dose; return to baseline levels within 48-72 hours following treatment discontinuation.
- Maximal lymphopenic effect observed by the 150 mg dose level (Figure 9), which was well tolerated over 7 days of dosing.
- Good safety profile, with most commonly reported treatment emergent adverse events (TEAEs) assessed as mild to intensity; two subjects in the single-dose Phase 1 studies, one at 150 mg QD and one at 250 mg (125 mg SD), developed an acute and transient right upper quadrant pain resembling biliary colic, accompanied by elevations in ALT and AST without concomitant elevation in bilirubin.
- No clinically significant changes in vital signs (including heart rate) or ECGs have been observed.

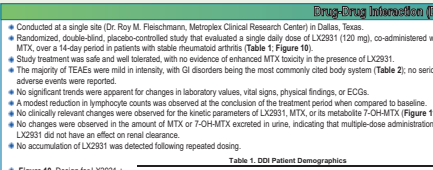
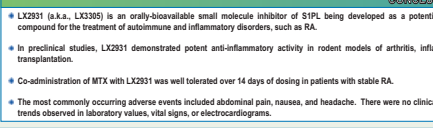


Table 1. DDI Patient Demographics

	LX2931 (n=12)	Placebo (n=2)	All Subjects (n=14)
Age (years)	Mean (SD)	59.8 (10.25)	58.7 (14.74)
	Median (min-max)	63.0 (55-70)	64.0 (43-70)
Gender (n, %)			
Female	12 (100.0%)	3 (100.0%)	15 (100.0%)
Race (n, %)			
Caucasian (White)	11 (91.7%)	3 (100.0%)	12 (80.0%)
Black or African American	3 (25.0%)	0 (0.0%)	3 (20.0%)
Hispanic or Latino Ethnicity (n, %)			
Yes	2 (16.7%)	0 (0.0%)	2 (13.3%)
No	10 (83.3%)	3 (100.0%)	13 (86.7%)
BMI at Screening (kg/m ²)	Mean (SD)	31.32 (7.778)	28.53 (7.006)
	Median (min-max)	29.85 (21.48-37)	28.20 (19.33-37)
DA58 CRP Score at Screening	Mean (SD)	2.647 (0.7421)	2.415 (1.4113)
	Median (min-max)	2.615 (1.16-3.88)	2.301 (1.24-3.88)



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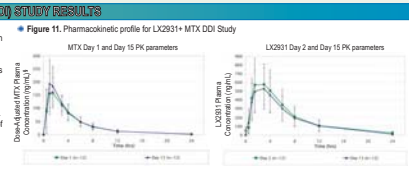
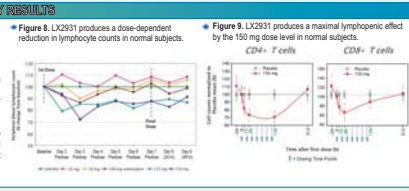


Table 2. DDI Treatment Emergent Adverse Event Summary

Body System Preferred Term	LX2931 Subjects, (%) (n=12)	Placebo Subjects, (%) (n=3)	Overall Subjects, (%) (n=15)
Gastrointestinal Disorders	5 (41.7)	0 (0.0)	5 (33.3)
General Disorders and Site Administration Conditions	4 (33.3)	0 (0.0)	4 (26.7)
Infections and Infestations	3 (25.0)	1 (33.3)	4 (26.7)
Nervous System Disorders	3 (25.0)	1 (33.3)	4 (26.7)
Musculoskeletal and Connective Tissue Disorders	2 (16.7)	1 (33.3)	3 (20.0)
Eye Disorders	1 (8.3)	0 (0.0)	1 (6.7)
Metabolism and Nutrition Disorders	1 (8.3)	0 (0.0)	1 (6.7)
Respiratory, Thoracic, and Mediastinal Disorders	2 (16.7)	0 (0.0)	2 (13.3)

CONCLUSIONS

- LX2931 (i.e., LX3305) is an orally-bioavailable small molecule inhibitor of S1PL, being developed as a potential therapeutic compound for the treatment of autoimmune and inflammatory disorders, such as RA.
- In preclinical studies, LX2931 demonstrated potent anti-inflammatory activity in rodent models of arthritis, inflammation and transplantation.
- Co-administration of MTX with LX2931 was well tolerated over 14 days of dosing in patients with stable RA.
- The most commonly occurring adverse events included abdominal pain, nausea, and headache. There were no clinically significant trends observed in laboratory values, vital signs, or electrocardiograms.
- No clinically significant changes in either MTX or LX2931 were observed.
- Inhibition of S1PL with a small molecule therapy, such as LX2931, represents a new mechanism for immune modulation with the potential to address inflammatory diseases such as RA.
- A Phase 2 study to determine the safety and efficacy of daily orally administered LX2931 in subjects with active RA on stable MTX therapy is currently ongoing.

DISCLOSURE: The authors of this poster are employees of, and have received stock options from, Lexicon Pharmaceuticals, Inc. The presenting author of this poster has received compensation from Lexicon Pharmaceuticals, Inc. both as a consultant and clinical investigator.