Preclinical Data Supporting the Differentiated Profile of STAR-0310, a Novel OX40 Antagonistic Monoclonal Antibody

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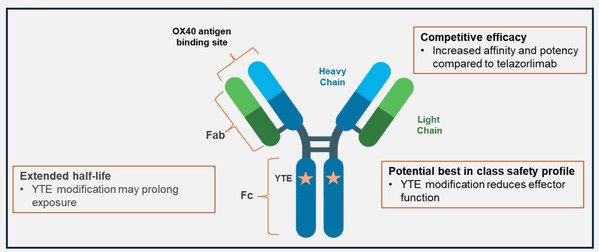
OBJECTIVES

- Preclinical experiments aimed to characterize STAR-0310, including affinity to human OX40, potency, effector function, and *in vivo* half-life **(Figure 1)**.

Figure 1. STAR-0310 Design[1,2]



SUMMARY

STAR-0310 IS AN INVESTIGATIONAL HIGH AFFINITY ANTI-OX40 ANTIBODY, WITH THE POTENTIAL TO BE BEST-IN-CLASS DUE TO:

1. **ENHANCED AFFINITY RESULTING IN SIGNIFICANT REDUCTION IN EFFECTOR T-CELL ACTIVITY AND CYTOKINE RELEASE INHIBITION.**
2. **REDUCED ADCC ACTIVITY (T CELL DESTRUCTION), THUS POTENTIALLY IMPROVING THE SAFETY PROFILE COMPARED TO OTHER OX40 ANTAGONISTS.**
3. **INFREQUENT DOSING FREQUENCY DUE TO THE DEMONSTRATED EXTENDED STAR-0310 SERUM MEAN HALF-LIFE OF 26 DAYS IN CYNOMOLGUS MONKEYS.**

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References:

1. Dall'Acqua WF, Kiener PF, Wu H. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). *J Biol Chem*. 2006 aug 18; 281(33):23514-24.
2. Booth BJ, Ramakrishnan B, Narayan K, Wollacott AM, Babcock GJ, Shriver Z, Viswanathan K. Extending human IgGhalf-life using structure-guided design. *MAbs*. 2018 Oct;10(7):1098-1110.

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INTRODUCTION

- Atopic dermatitis (AD) is a chronic, relapsing-remitting inflammatory skin disease that has a significant impact on quality of life.
- Acute phases of AD involve a notable modulation of Types 1, 2, and 3 immune responses where OX40 receptor plays a key role.
- The co-stimulatory T-cell receptor OX40 is primarily expressed on activated effector and regulatory T-cells. Its ligand, OX40L, is present on activated antigen-presenting cells, including dendritic cells, endothelial cells, macrophages, and B-cells.
- Engagement of OX40 with OX40L is crucial for the proliferation and survival of T cells and upregulation of cytokine production.

METHODS

- **Binding affinity:** Surface plasmon resonance was used to measure binding affinity of STAR-0310 to human OX40.
- **Cytokine-release inhibition assay:** STAR-0310 potency was assessed by a cytokine release inhibition assay. T cells were pre-activated for 24 hours using coated OKT3 and soluble CD28, then incubated with co-coated OKT3 and OX40L in the presence or absence of treatments. All molecules were 1/3 serially-diluted starting at 200 nM with control isotypes at 200 nM. Supernatants were harvested on day 4, then quantified using Meso Scale Discovery assays.
- **Antibody-dependent cellular cytotoxicity (ADCC) assay:** STAR-0310 effector function was measured by ADCC assay. Activated or regulatory T cells were co-cultured with autologous natural killer cells in the presence of treatments starting at 20 nM and diluted by 5 or control isotypes at 20 nM. The percentage of ADCC was measured by lactate dehydrogenase release after 4.5 hours of incubation.
- Statistical analysis was performed using paired one-way ANOVA, followed by Tukey's post-hoc test (ns $p>0.05$, * $0.05>p>0.01$, ** $0.01>p>0.001$). Graphs show 6 (activated T cells) or 8 (regulatory T cells) donors, 3 independent experiments.

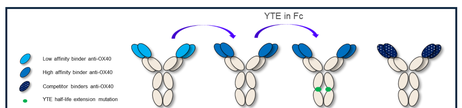
RESULTS

STAR-0310 SHOWS ~8X FOLD INCREASE OF BINDING AFFINITY TO HUMAN OX40 COMPARED TO STAR-0305

STAR-0310, an affinity-matured, YTE-modified derivative of telazorlimab (STAR-0305), demonstrates an approximately 8-fold enhancement in binding affinity to human OX40 **(Figure 2).**

STAR-0310 retains similar binding affinity to human OX40 as STAR-0308, which lacks the YTE modification, suggesting that the YTE modification does not influence the binding affinity of the molecule.

Figure 2. The binding affinity of STAR-0310 to human OX40 measured by SPR



Name	STAR-0305 (telazorlimab)	STAR-0308	STAR-0310	AMG451 (rocatinlimab)[a]
Description	Parent molecule	Affinity maturated	Affinity matured with YTE	comparator
IgG1 backbone modification	N/A	N/A	YTE	Afucosylation
Binding affinity K_D (nM)	59.3 ± 2.0	6.8 ± 0.2	7.2 ± 0.4	3.0 ± 0.4

STAR-0310 REDUCES OX40L-INDUCED CYTOKINE PRODUCTION

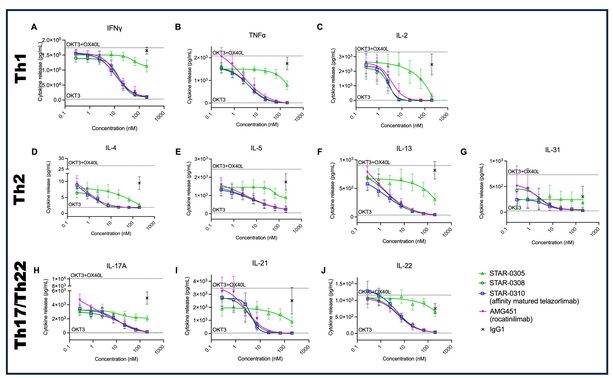
Figure 3 shows cytokine secretion dose-response curves of cytokine secretion inhibition.

Enhanced affinity to OX40 in STAR-0308 results in a dramatic reduction of cytokine release compared to STAR-0305**.**

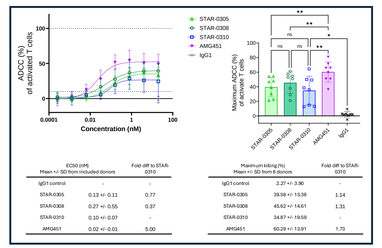
The YTE mutation in STAR-0310 doesn't appear to affect the potency.

The potency of STAR-0310 in cytokine release inhibition is comparable to AMG451.

Figure 3. STAR-0310 Potency in Cytokine-release Inhibition Assay



STAR-0310 INDUCES SIGNIFICANTLY LOWER ADCC ON ACTIVATED (FIGURE 4) AND REGULATORY (FIGURE 5) T CELLS COMPARED TO AMG451

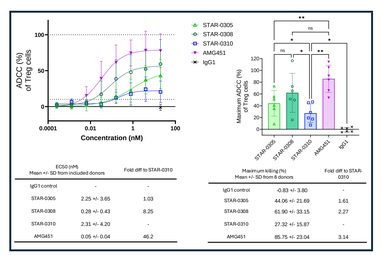


EC50 (nM) Mean +/- SD from included donors		Fold diff to STAR-0310
IgG1 control	-	-
STAR-0305	0.13 +/- 0.11	0.77
STAR-0308	0.27 +/- 0.55	0.37
STAR-0310	0.10 +/- 0.07	-
AMG451	0.02 +/- 0.01	5.00

Maximum killing (%) Mean +/- SD from 8 donors		Fold diff to STAR-0310
IgG1 control	2.27 +/- 3.90	-
STAR-0305	39.58 +/- 13.38	1.14
STAR-0308	45.62 +/- 14.61	1.31
STAR-0310	34.87 +/- 19.59	-
AMG451	60.29 +/- 13.91	1.73

Figure 4. STAR-0310 Effector Function on Activated T-cells

- STAR-0310 showed less activated T cell destruction compared to AMG451, which demonstrated a 5-fold greater killing capacity.
- STAR-0310 showed ~75% lower maximal killing on activated T cells relative to AMG451.



EC50 (nM) Mean +/- SD from included donors		Fold diff to STAR-0310
IgG1 control	-	-
STAR-0305	2.25 +/- 3.65	1.03
STAR-0308	0.28 +/- 0.43	8.25
STAR-0310	2.31 +/- 4.20	-
AMG451	0.05 +/- 0.04	46.2

Maximum killing (%) Mean +/- SD from 8 donors		Fold diff to STAR-0310
IgG1 control	-0.83 +/- 3.80	-
STAR-0305	44.06 +/- 21.69	1.61
STAR-0308	61.90 +/- 33.15	2.27
STAR-0310	27.32 +/- 15.87	-
AMG451	85.75 +/- 23.04	3.14

Figure 5. STAR-0310 Effector Function on Regulatory T-cells

- STAR-0310 exhibits 46-fold lower elimination of regulatory T cells than AMG451.
- The incorporation of the YTE mutation in STAR-0310 results in statistically lower maximal cytotoxic activity against regulatory T cells, relative to STAR-0305 and STAR-0308.

STAR-0310 EXHIBITS PROLONGED PLASMA $T_{1/2}$ IN CYNOMOLGUS MONKEYS (FIGURE 6)

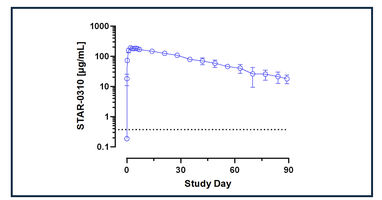


Figure 6. PK studies of STAR-0310 in cynomolgus monkeys

- Single dose *in vivo* pharmacokinetic data from cynomolgus monkeys dosed with 20 mg/kg STAR-0310 via subcutaneous route (N = 3); data represent STAR-0310 mean concentration over time.
- The mean STAR-0310 half-life in cynomolgus monkey was 26 days.

CONCLUSIONS

- STAR-0310's favorable preclinical profile supports further development of STAR-0310 for the treatment of moderate-to-severe atopic dermatitis and other immunologic diseases.
- The extended half-life suggests potential for sustained efficacy and prolonged suppression of disease symptoms.

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