SHATTUCK LABS

Preclinical Development of SL-325, a High Affinity DR3 Blocking Antibody, for Durable Blockade of the TL1A/DR3 Axis in Inflammatory Bowel Disease

European Crohn's and Colitis Organization – 2025

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Nasdaq: STTK

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Forward-Looking Statements

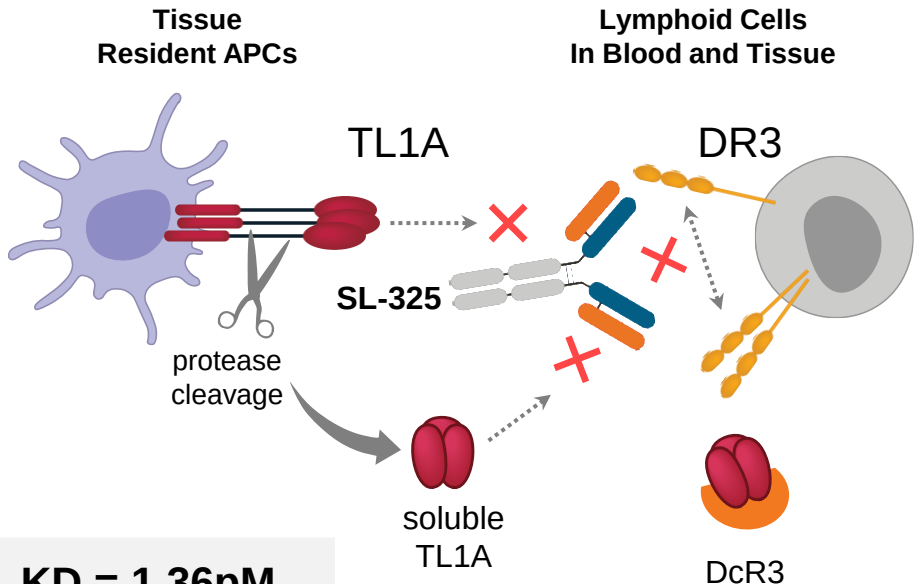
This presentation contains “forward-looking statements” within the meaning of the federal securities laws, which statements are subject to substantial risks and uncertainties and are based on our estimates and assumptions. All statements, other than statements of historical facts included in this presentation, are forward-looking statements, including statements concerning: our plans, objectives, goals, strategies or intentions relating to products and markets; the potential purity, potency and clinical benefits of our product candidates, including SL-325; the anticipated timing of an IND filing for SL-325; the anticipated timing and design of our planned Phase 1 clinical trial of SL-325 and the anticipated timing for data and the association of preclinical data with potential clinical benefit. In some cases, you can identify forward-looking statements by terms such as “may,” “might,” “will,” “objective,” “intend,” “should,” “could,” “can,” “would,” “expect,” “believe,” “design,” “estimate,” “predict,” “potential,” “plan,” or the negative of these terms, and similar expressions intended to identify forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors that could cause our actual results to differ materially from the forward-looking statements expressed or implied in this presentation, in addition to those risks and uncertainties, such as global macroeconomic conditions and related volatility; expectations regarding the initiation, progress, and expected results of our preclinical studies, clinical trials and research and development programs; expectations regarding the timing, completion and outcome of our clinical trials; the unpredictable relationship between preclinical study results and clinical study results; the timing or likelihood of regulatory filings and approvals; our expectations regarding the overall benefit of the strategic prioritization of our pipeline; liquidity and capital resources; and other risks and uncertainties described in “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K (File No. 001-39593) for the fiscal year ended December 31, 2023 and elsewhere in such filing and in our other periodic reports and subsequent disclosure documents filed with the U.S. Securities and Exchange Commission.

We cannot assure you that we will realize the results, benefits or developments that we expect or anticipate or, even if substantially realized, that they will result in the consequences or affect us or our business in the way expected. Forward-looking statements are not historical facts, and reflect our current views with respect to future events. Given the significant uncertainties, you should evaluate all forward-looking statements made in this presentation in the context of these risks and uncertainties and not place undue reliance on these forward-looking statements as predictions of future events. All forward-looking statements in this presentation apply only as of the date made and are expressly qualified in their entirety by the cautionary statements included in this presentation. We have no intention to publicly update or revise any forward-looking statements to reflect subsequent events or circumstances, except as required by law.

We obtained the data used throughout this presentation from our own internal estimates and research, as well as from research, surveys and studies conducted by third parties. Internal estimates are derived from publicly available information released and our own internal research and experience, and are based on assumptions made by us based on such data and our knowledge, which we believe to be reasonable. In addition, while we believe the data included in this presentation is reliable and based on reasonable assumptions, we have not independently verified any third-party information, and all such data involve risks and uncertainties and are subject to change based on various factors.

This presentation concerns a discussion of investigational drugs that are under preclinical and/or clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration. They are currently limited by Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

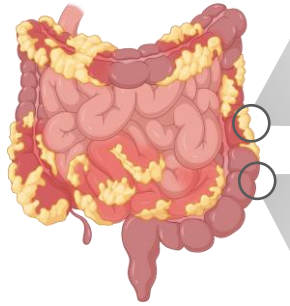
SL-325 Is a High-Affinity DR3-Specific Blocking Antibody

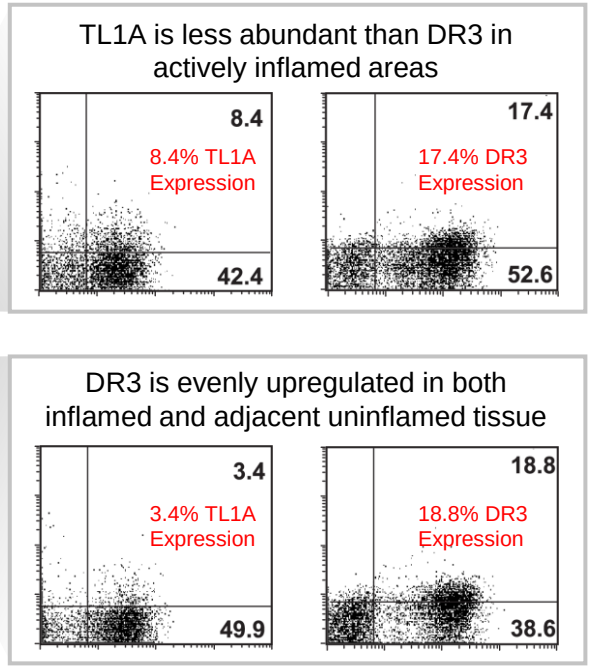


KD = 1.36pM

IC_{50} = 0.8nM

Crohn's Disease is characterized by discontinuous and migratory inflammation

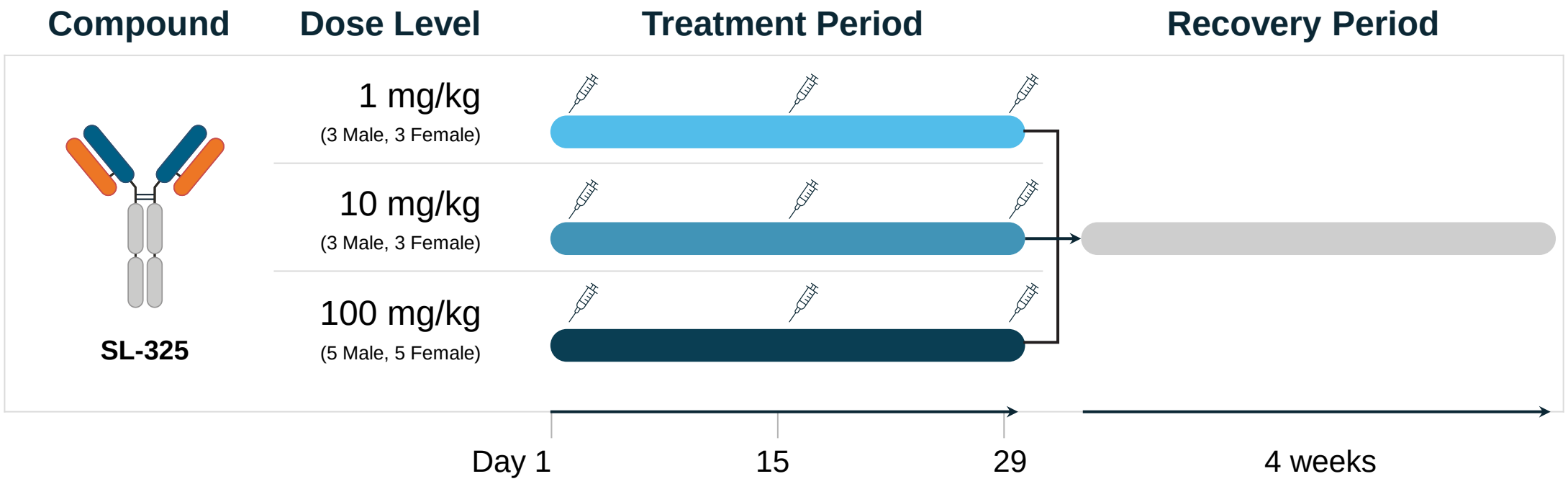




DR3 is constitutively expressed by lymphocytes both at involved and uninvolved areas of the gut

➔ DR3 is more abundant, constitutively expressed. and evenly upregulated in involved and adjacent uninvolved GI tissue in UC and Crohn's Disease that TL1A, providing rationale as a better target for TL1A inhibition

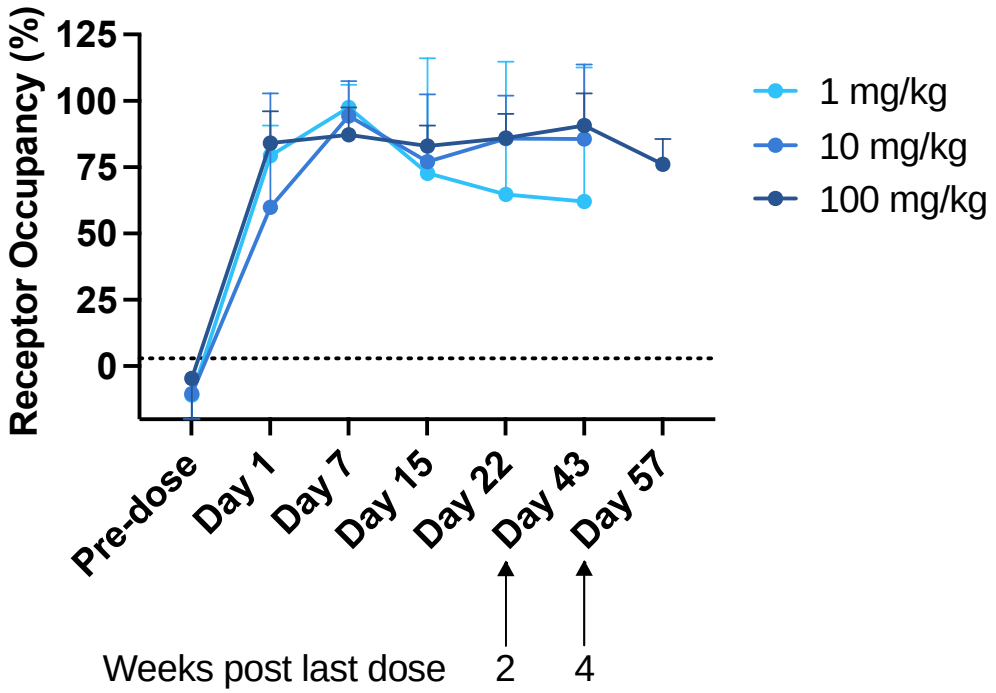
SL-325 NHP Study Design and Safety Overview

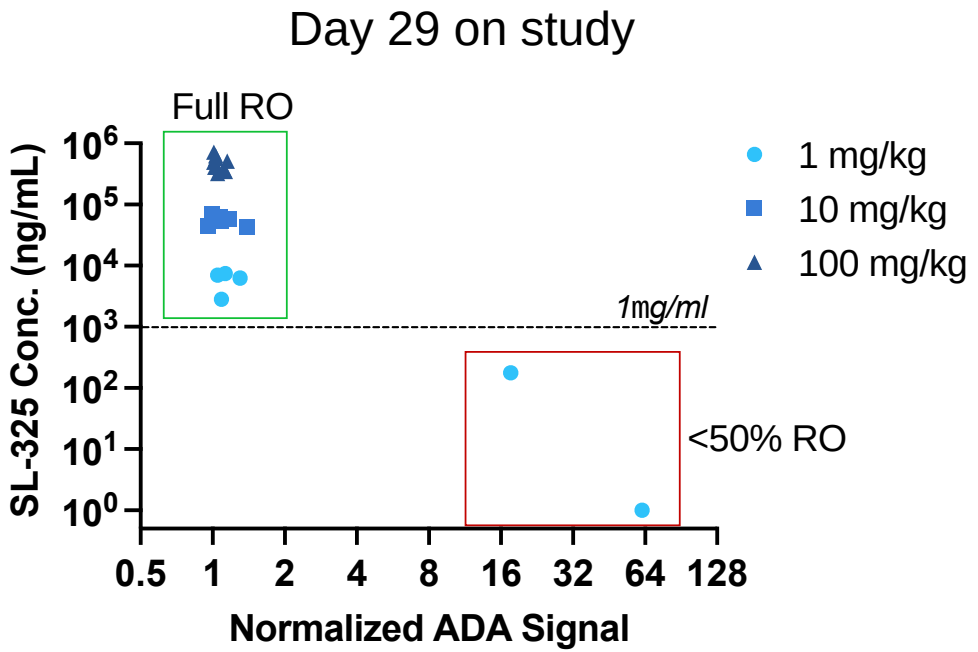


- IND-enabling GLP toxicology study in cynomolgus macaques
- No-observed-adverse effect level (NOAEL) is the top dose of 100 mg/kg
- No changes in clinical pathology parameters, gross pathology, or histopathology analysis observed

Vehicle controlled group, n=10 in the NHP study
Study endpoints: Safety, PK analysis, DR3 RO, ADA analysis, peripheral immunophenotyping and terminal histopathology analysis
RO= Receptor Occupancy

SL-325 Achieved Full and Durable Receptor Occupancy (RO)

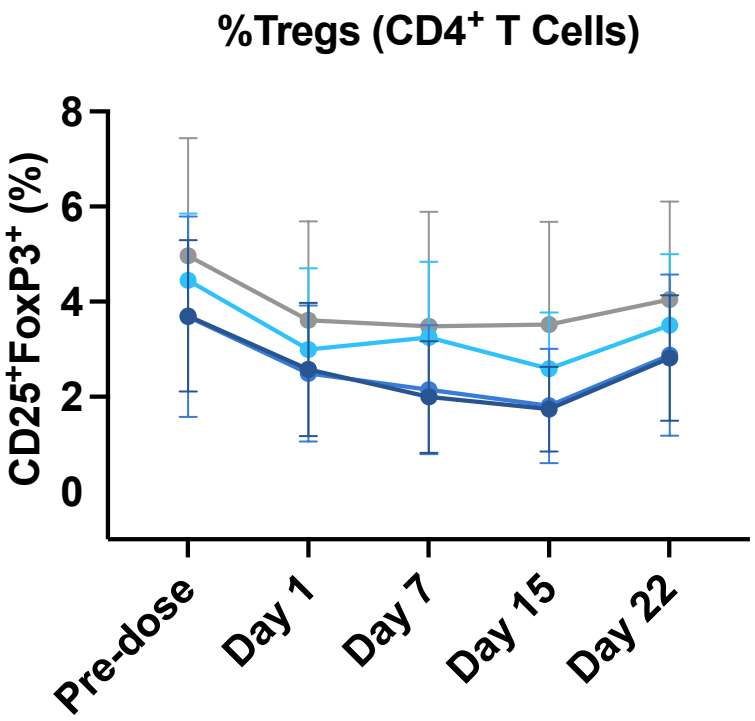


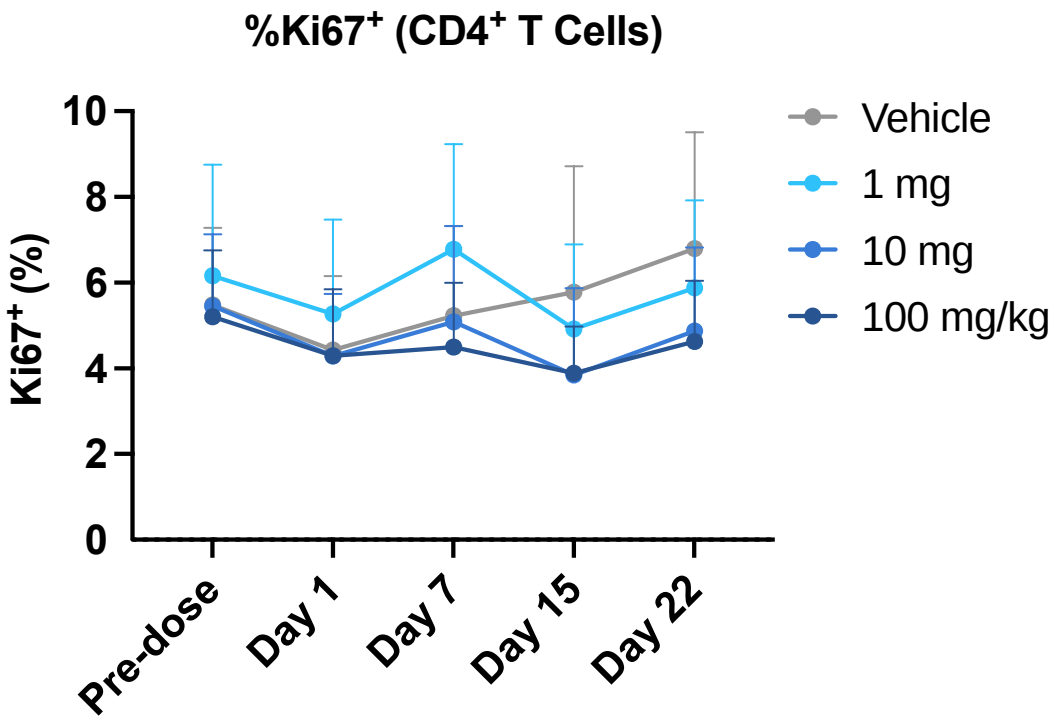


- Full DR3 RO was observed at all dose levels, and binding was durable for at least four weeks post-dose
- In two animals that developed ADA, a drop in DR3 RO was observed, suggesting trough concentrations ≥1 µg/mL maintain full RO

This slide shows preliminary data and analysis available to Shattuck as of the February 6, 2025.

SL-325 Showed No Signs of DR3 Agonism



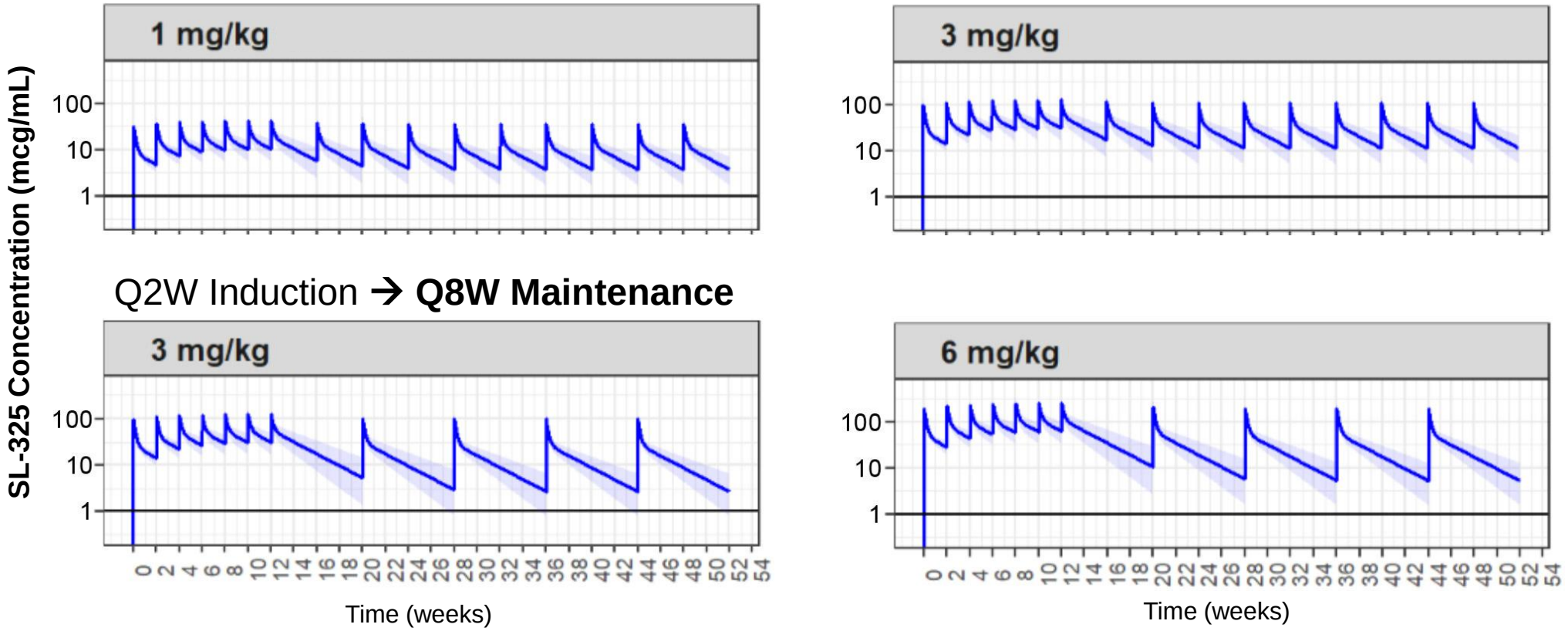


- DR3 activation causes rapid proliferation of T cells (Treg and antigen-activated Tcon)
- Peripheral blood flow cytometry confirmed that there was no evidence of T cell proliferation in any treated animal

This slide shows preliminary data and analysis available to Shattuck as of the February 6, 2025.

Projected Dose and Schedule in Human Subjects

Q2W Induction → **Q4W Maintenance**



➔ 3 - 6 mg/kg dosing at Q2W induction and Q4-8W maintenance expected to provide Ctrough concentration > 1 µg/mL to achieve full RO in peripheral blood

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SL-325 Expected to Enter Clinical Development in 2025 as a First-In-Class DR3 Blocking Antibody

Favorable Safety Profile

- ✓ NOAEL is the top dose of 100 mg/kg
- ✓ No IRRs observed
- ✓ No changes in clinical pathology parameters, gross pathology, or histopathology analysis observed

Full RO and Lack of DR3 Agonism

- ✓ Full RO starting at 1 mg/kg, durable for > 28 days
- ✓ No Treg expansion or activation of CD3 T Cells observed

Differentiation from TL1A Blocking mAbs

- ✓ Immune complex formation and stabilization of TL1A not expected
- ✓ Durable blockade of constitutively expressed DR3 may translate to higher complete remission rates
- ✓ Distinct profile for bispecific antibody development

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Thank You

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