Treatment with LBL-051-S3, a CD3/CD19/BCMA trispecific antibody, leads to a complete loss of plasma cells and B cells with minimal cytokine release in non-human primates

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INTRODUCTION

Autoimmune diseases arise from breakdowns in immune tolerance that lead to inappropriate production of autoantibodies and chronic tissue inflammation. Although current therapies, including biologics and targeted small molecules, can suppress broad immune pathways, many patients fail to achieve durable disease control or experience dose-limiting toxicities, underscoring the need for additional treatment options. Recently, administration of CAR-T cell therapies targeting CD19 and/or BCMA have resulted in long-term, drug-free remission of patients with autoimmune disorders (1, 2). CD19 and BCMA are complementary targets and early clinical data with dual targeting CAR-T cells has demonstrated superior autoantibody clearance (3); however, these therapies carry significant safety risks and patient access challenges. Dual targeted T cell engager molecules are poised to enter the clinic and show promise in achieving a safe and accessible treatment option for patients with refractory autoimmune disorders.

AIM

To analyze the effects of treatment with a trispecific antibody targeting CD3, CD19, and BCMA in nonhuman primates.

METHODS

LBL-051 is a novel, next-generation, trispecific T cell engager antibody which binds CD3, CD19, and BCMA with optimized affinity to minimize cytokine release while maximizing B and plasma cell depletion. LBL-051 lacks cross-reactivity with analogous cynomolgus targets, requiring the use of a surrogate molecule, LBL-051-S3, with comparable binding affinities in cynomolgus monkey studies.

LBL-051-S3 was administered to animals subcutaneously in a single or two-dose step up regimen, and animals were followed for a minimum of 28 days. Step-up doses were chosen to maximize B cell depletion while minimizing cytokine release syndrome (CRS). The priming dose was chosen at a level where no CRS symptoms were observed in any animals, and complete peripheral B cell depletion was achieved.

Pharmacodynamic biomarkers were evaluated across some dose groups including peripheral B cell depletion and recovery via flow cytometry, CD19+ B cell depletion in bone marrow, lymph nodes, and spleen using flow cytometry and IHC, depletion of plasma cells in the bone marrow by flow cytometry, ELISA measurement of post-dose cytokine panel, and immunoglobulin levels.

ACKNOWLEDGEMENTS

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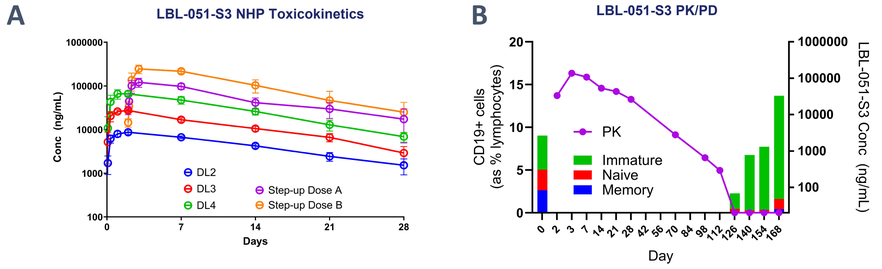
RESULTS

Precise correlation between PK and duration of B cell depletion

Figure 1. (A) Pharmacokinetic (PK) profiles of LBL-051-S3 at single dose level (DL) and step-up dose regimens, n=6 per group. (B) Representative profile of LBL-051-S3 PK and peripheral B cell composition in a single animal treated with step-up Dose A of LBL-051-S3. B cell gating (CD3-/CD16-/CD19+): Immature (/CD21-), Naïve (/CD21+/CD27-) Memory (/CD21+/CD27+)



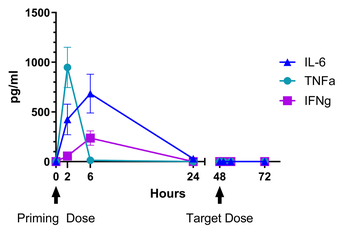
No CRS observed with step-up dosing regimen

Figure 2. (A) Incidence of cytokine release syndrome (CRS) in animals treated with LBL-051-S3 at increasing doses. n=6 animals per group. (B) LBL-051-S3 was administered at Day 0 (priming dose) and 48 hours later (target dose) using Step-up Dose A. Cytokines were measured at 0, 2, 6 and 24 hours following each dose. Similar results were observed with the higher Step-up Dose B.

A

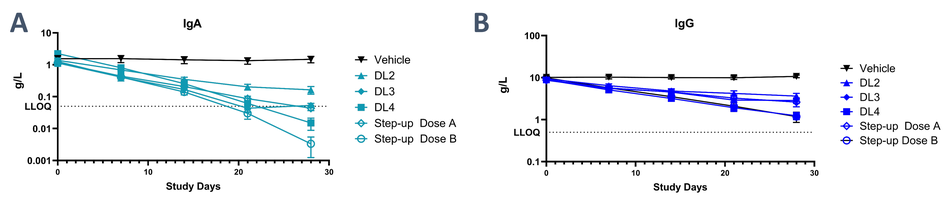
Dose (mg/kg)	Grade 1 CRS	> Grade 1 CRS
DL1	0/6	0/6
DL2	0/6	0/6
DL3	0/6	0/6
DL4	2/6	0/6
Step-up Dose A	0/6	0/6
Step-up Dose B	0/6	0/6

Grade 1: transient fever
Grade 2+: follows ASTCT CRS grading[4]
DL: Dose Level; CRS: Cytokine release syndrome



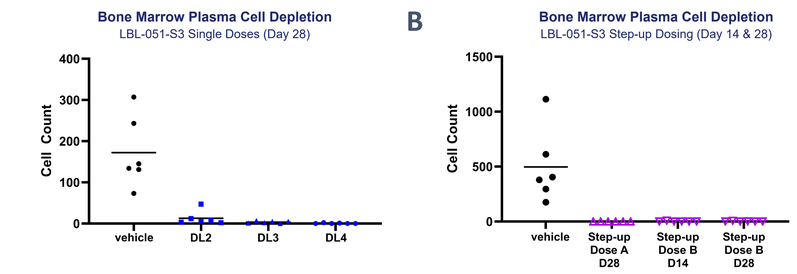
IgA levels are decreased below LLOQ in peripheral blood

Figure 3. As a surrogate for antibody-secreting cell function, circulating levels of (A) IgA or (B) IgG were measured in the peripheral blood of animals treated with LBL-051-S3 at the indicated dose levels (DL) on Days 7, 14, 21 and 28. LLOQ, lower limit of quantitation.



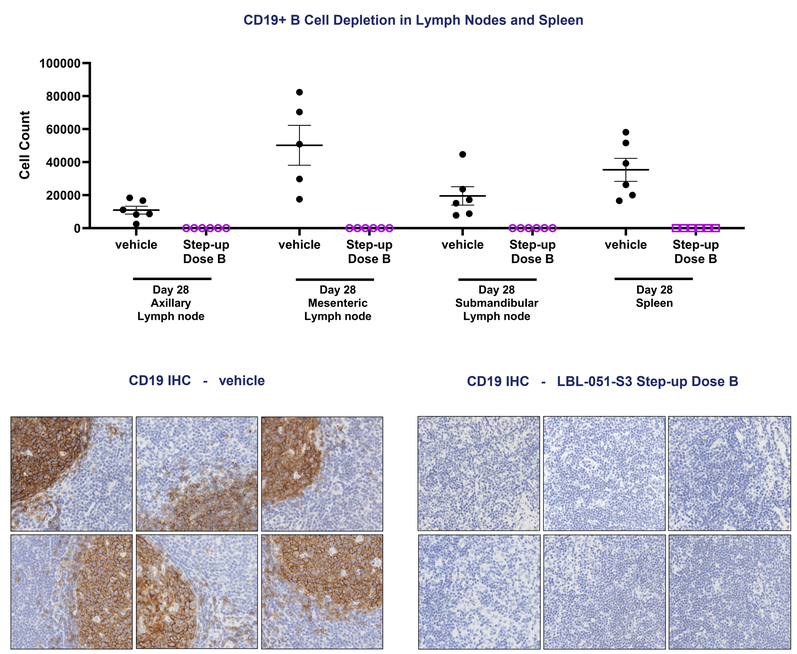
Complete depletion of plasma cells in the bone marrow

Figure 4. Plasma cells were defined as CD3-/CD14-/CD19-/CD20-/CD38+/CD138+ and analyzed by flow cytometry in the bone marrow at (A) Day 28 in single dose groups, and (B) Day 28 in the Step-up Dose A group and Days 14 and 28 in the Step-up Dose B group



Complete depletion of B cells in the lymph nodes and spleen

Figure 5. (A) CD19+ B cells were analyzed by flow cytometry in lymph node and spleen tissues in the Step-up Dose B group at Day 28. (B) Submandibular lymph node tissue was stained for CD19+ B cells using immunohistochemistry. Each image is representative of a single animal from the Step-up Dose B group or the control group.



CONCLUSIONS

- LBL-051-S3 rapidly and completely depletes peripheral B cells at all doses and completely depletes both peripheral and tissue B cells and plasma cells in cynomolgus monkeys at step-up Dose A and higher for a minimum of 28 days.
- No CRS was detected using the step-up treatment regimen with LBL-051-S3 while increasing exposure.
- Dose dependent decreases in immunoglobulins were observed with LBL-051-S3 treatment, indicative of a loss of antibody-secreting plasma cells.
- Our data demonstrating four months of peripheral B cell depletion with subsequent recovery of predominantly immature B cells suggests that targeting both CD19 and BCMA with a T cell engager molecule could be an optimal strategy to achieve immune reset.

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